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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953.
2. Humphreys, P., *et al.*: Angiology *3*:1 (Feb.) 1952.
3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

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1. Freis, E.D., Finnerty, F.A., Jr., Schnaper, H.W., and Johnson, R.L.: *Circulation* **5**:20, Jan. 1952.

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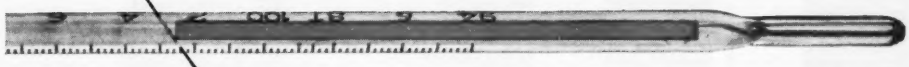

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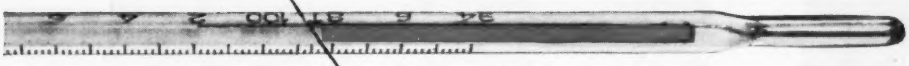

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1. Flippin, H. F.: Philadelphia Med. *49*:733 (Jan. 30) 1954.
2. Glatt, M., and Ross, S.: Antibiotics & Chemotherapy *4*:395 (Apr.) 1954.

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AUTHORS	No. of Patients	Chronic, Resistant to Other Therapy	TYPES OF ULCERS				RELIEF OF SYMPTOMS (Chiefly Pain)				Surgery or Complications[1]	Side Effects Requiring Discontinuance of Drug[2]	EVIDENCE OF HEALING			
			Duodenal	Jejunal	Stomal	Gastric	Good	Fair	Poor	No Report			Complete	Moderate	None	No Report
Grimson, Lyons, Reeves	100	100	93	7			80	11	4		5		47		19	29
Friedman	15	15	14			1	5		4	6[3]			2			13
Bochgaard, Nielsen, Bang, Gravelund, Tobiassen	26	26	21			5	16	4	6				8	6	12	
McHardy, Browne, Edwards, Marek, Ward	162		162				136	12	11		3	1	14	9	7	129
Segal, Friedman, Watson	34	34	34[4]				14	13			7	2	5		8	14
Brown, Collins	117	99	117				97	7	8		5	8	55	9	8	40
Asher	77		65		7	5	52	9	16			16		9	21	47
Rodriguez de la Vega, Reyes Diaz	5	4	5				4		1					3	2	
Winkelstein	116	116	102	8		6	102		14				53		18	45
Hall, Hornisher, Weeks	18	18	18				11		1	6[5]			18			
Maier, Meili	38	38	24			14[6]	27	7	4[7]				10	2	5	21
Meyer, Jarman	25	18	25				21		4							25
Poth, Fromm	37	37	37				33	3	1				33	3	1	
Plummer, Burke, Williams	41	41	41				36		5				38		3	
McDonough, O'Neil	104	100	104				63	10	31			11	4		11	89
Broders	60	60	58		1	1	35	19	6				10	1	49[8]	
Legerton, Texter, Ruffin	11		11				11									11
Holoubek, Holoubek, Langford	76	69	76				35	27	10		4	10	26		10	36
Ogborn	42		39	2		1	42[9]									42
Shaiken	48	48	48				33	10	3		2		33	10	3	
Johnston	145	145	145				143		2			2	143		2	
Rossett, Knox, Stephenson	146		141			5	146					4[10]	53			93
TOTALS	*1443*	*968*	*1380*	*17*	*8*	*38*	*1142*	*132*	*131*	*12*	*26*	*54*	*552*	*52*	*179*	*634*
PERCENTAGES		*67.8*	*95.6*	*1.2*	*0.6*	*2.6*	*81.3*	*9.4*	*9.3*			*3.7*	*70.5*	*6.6*	*22.9*	

1. Not included in tabulations.
2. Included in "Relief of Symptoms" as "Poor" and in "Evidence of Healing" as "None."
3. Four had no symptoms when Banthine therapy was begun.
4. Of which seven were penetrative lesions and five partially obstructive.
5. No symptoms were present in four.
6. Two with symptoms only; no demonstrable ulcer.
7. Three were psychopathic patients and one had a ventricular ulcer of the lesser curvature.
8. Roentgen findings after treatment period of two weeks; forty-seven had duodenal deformity.
9. All returned to work within a week.
10. In these four, after relief of symptoms, Banthine was discontinued because of urinary retention.

During the past three years, more than 250 references to Banthine therapy in peptic ulcer and other parasympathotonic conditions have appeared in medical literature. Of these reports, 22 have presented specific facts and figures on the results of treatment in a total of 1,443 peptic ulcer patients, 67.8 per cent of whom were reported as chronic or resistant to other therapy. These results are tabulated above and show:

"Good" relief of symptoms was obtained in 81.3 per cent of the 1,405 patients on whom reports were available.

"Complete" evidence of healing was obtained in 70.5 per cent of the 783 patients on whom reports were available.

In all but 9.3 per cent, relief of pain was "good" or "fair." In all but 22.9 per cent, evidence of healing was "complete" or "moderate."

During treatment, 26 patients required surgery or developed complications other than ulcer which required discontinuance of the drug before results could be evaluated.

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VOLUME 94 JULY 1954 NUMBER 1

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Editorials

TIMIDITY AND CAVEATS

WE ARE children of uncertainty. We live in an age which strives frantically for comfort and reassurance that all is well. While seeking the absolute, we are fearful of error and uncertain of truth. As medical organizations form, as bureaus multiply, as journals proliferate, as size increases, a sense of personal or corporate responsibility suffers from a corrosive rusting outside and a caseating crumbling away inside. Rarely do we challenge or even look at our own fixed habits. Let me examine briefly this phenomenon as it applies to medical journalism, particularly the reporting of research, the writing of editorials, and the art of reviewing books or new advances.

The editor and board of editors of medical journals have many responsibilities —to advance knowledge, to disseminate information, to present facts, interpretations, and their implications and impacts. No thoughtful reader expects to agree with everything he reads. He wants honest facts, honestly presented. He needs data that he may view clearly and draw his own conclusions. Today's practice may be tomorrow's folklore and must be if medicine continues to move along. Expecting honesty but not perfection, how strange it is to open a journal or copy of transactions and read, in effect, "We assume no responsibility for the statements and opinions of the papers read at our meetings." This can be viewed as a vote of no confidence in those who select the program or a confession of doubt of the sense or integrity of those who present papers. How flattering is the implication—behind these weasel words lurk our best efforts. This *caveat lector*, reader beware, is a demoralizing tribute to the ultraconservative anxiety of reaction, timidity, and the unnecessary lip service of youth to age. If a society or a journal does not have responsibility to its readers, what right does it have to print? This is not to say that everything is "authoritative" or "true" or "final" but that it is the best that the writer can do honestly. We must recognize and allow for shifting in the corpus of truth as time moves its center of gravity.

The large contributions to contemporary medical knowledge made by the National Institutes of Health, the Veterans Administration, the Army, the Navy, the gifts of industry, and the sustenance from benevolent foundations and persons deserve praise and recognition. No one begrudges the tip of the hat in a footnote or the curtsy of a kind word of acknowledgment. But is it not remarkable how this is repaid by a deft kick on the shins when the supporter of the investigator says in effect, "I helped him if he is right, I don't know him if he is wrong, and I don't really understand it. Anyhow, it probably won't make any difference and does not necessarily reflect the opinion or policy of this agency, assuming we have any opinion or policy."

No sensible person expects the supporter of research to understand everything that is done. In selecting an investigator trusted for honesty and imagination on the best available information, i. e., a close scrutiny of the recent past, the supporting agent or person has fulfilled his function. Neither veto nor censorship belong to him. Editors must decide on the utility, reliability, and pertinence of the papers published. Their publication implies acceptability on the basis of the best judgment available, not the illusion that absolute truth is enthroned.

In present day American medical journalism we have seen mercifully the decline of the bitter personal polemic because the notion that professors, department heads, and "authorities" are infallible has vanished with the atrophy of pontification from the corrections supplied by exact technical procedures. In bygone days the clinician ran the risk of definitive contradiction only once—at the autopsy table. Today it may recur in one case a dozen times from the cold technics of the laboratory. Not having to keep up the pretense of perfection, it is easier to admit error, or apply the continual adjustments of interpretation as understanding grows. But authority dies hard, and few of us can altogether avoid suspecting the good will of someone we disagree with or admiring inordinately anyone who confirms us in data or dogma.

The problems of editorials, book reviews, and journals of review and opinion are many and vexing. Ideas are not generated amorphously in some collective editorial or reviewer's committee brain; they must be the work of one person to have any critical value. This person should not hide under the editorial smoke screen of a board of editors or the blank anonymity of no board at all. There are many useful ideas in critical or speculative editorials, but they should be signed. Perceptive readers might want to continue the discussion, disagree or agree. Nothing is more frustrating than to read some anonymous proclamation and have no target for praise or blame. No really sensible person expects a book review to do more than express one opinion. Critical and thoughtful reviews might give some corrective to the increasing scum of books containing only the redeposited froth and bubbles so easily collected from other flotsam. But criticizing anyone's book or paper is like telling a mother that her baby is ugly. Regardless of opinion, when one feels obliged to do it he should not do it under the protection of anonymous letters, and he should be prepared to face the consequences. Current texts and most scientific writing show the sad results of the absence of any consistent forum of criticism to elevate tone, improve style, clarify methods, and advance scholarship.

Consider for a moment some of the warnings of poisoned water which greet us when we open a journal or book.

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This uncouth habit of disclaimers may have arisen from uncertainty, from timidity, or from fright. If one chooses an analogy it is ready at hand in the storm warnings found at the beginning of many plays. I have taken several from the delightful dramas of Dr. Mavour, late professor of medicine at Glasgow, who wrote under the pseudonym of James Bridie.

"The characters and incidents in this play are entirely imaginary."

"None of the characters or incidents in this play is intended to suggest actual individuals or happenings. Nor is the play intended as a satire upon any actual society or group of people. It is to be read and played purely as a work of imagination."

"No reference is intended to any living person or any current event."

I would not criticize a professor of medicine for writing dramas under the inky cloud of a pen name. And the introductory caveat, however much it suggests a false claim, is an aid against libel. As such, there is a good reason for its use by dramatists or fiction writers. I see no reason, however, to have similar warnings in medical journals unless one suspects borrowing, plagiarism, or falsehood, and then it is the responsibility of the editors not to publish.

I have written two papers which had these footnotes:

"Prepared at the direction of the Commanding General, Army Ground Forces, at the Medical Research Laboratory, Fort Knox, Kentucky."

Here is the assurance of confidence and trust with no quibble; no if's, and's, or but's. The other is self-explanatory:

"This work was supported by no grant and reviewed by no committee. No hallmark pronounces its auspices, claims credit for whatever merit it may have while disclaiming any responsibility. It expresses no policy and aims its ironic barbs carefully but without malice."

Is the introductory admonition needed to prevent the misinterpretation of published medical scientific papers? Will the quotation warped out of context, the testimonial innuendo, the seal and sanction of authority decline as abuses only if the note of caution is sounded by the ambivalent sponsor? I doubt it. In a recent discussion with several medical investigators and editors whose opinion I hold in high regard I was astonished at the expression of fear that such abuse would flourish if the lookout sign were taken down. Perhaps my own existence in an atmosphere so lacking in the authoritarian attitude spoils my objectivity. The mass of

practicing physicians may indeed attune their ideas and harmonize their practice to the latest quiver of the baton of the authority of the "seal of approval" of this body, this foundation, this journal, this bureau, this author. My experience is that if judgment is so poverty-stricken, it is the influence of the printed word upon the merely literate rather than the symbol of authority and testimonial of certainty on the inquiring mind which is at fault.

The reliance on authority characterized the long empty years in medicine before clinical observation led its pioneers into the laboratory to search for better understanding of problems of rich and challenging perplexity. Dogma was enthroned. The master's word was law. But in a short time we have come a long way from such a static and rigid formula. Research, by reorienting and forever changing our understanding, has some hope of freeing the intellect from dependence on dogma. Man's quest for certitude is doomed to disappointment by the nature of the hunter and the hunted. Final certainty is an illusion which serves a useful purpose only if it is an accelerator rather than a brake in our search for wisdom. In the nature of writing, editing, and printing we must preserve freedom within the boundaries of clarity, objectivity, and honesty without assuming a guarantee of eternal and unchanging "truth."

And finally I expect these views to stir up honest and fruitful disagreement. They are not the last word.

WILLIAM B. BEAN, M.D.

CONTRIBUTIONS OF RICHARD BRIGHT AND HIS ASSOCIATES TO RENAL DISEASE

NORMAN M. KEITH, M.D.
AND
THOMAS E. KEYS, M.A.
ROCHESTER, MINN.

TO DISCUSS properly the contributions of Richard Bright and his associates to present knowledge of diseases of the kidney, it is necessary to review briefly the setting in Great Britain in the first thirty years of the nineteenth century. This period was marked by the triumphant campaigns of Wellington against Napoleon, by the flowering of artistic and inventive genius, by the gaudy excesses of the rich and the consequent suffering of the poor. Britain, without realizing what was happening, was undergoing a major shakeup, and the sudden advent of the industrial revolution almost brought about a rebellion. Consequently, the end of the third decade of the nineteenth century was a period of political and social turmoil. Happily, liberal politicians were in the ascendant in parliament, and they succeeded in enacting important reforms. Among these were a democratic electorial law and passage of an anatomy bill which permitted dissection of the human body. Both these laws were supported strenuously in parliament by the youthful liberal lawyer and man of letters, Thomas Babington Macaulay.* Among the physicians of note at that period in London were Richard Bright, Thomas Addison, and Thomas Hodgkin. These physicians, like Macaulay, were active reformers, and their contributions to the advancement of medicine paralleled the liberal achievements of their political contemporaries.

Of the afore-mentioned physicians, it seems to us, as it seemed to a contemporary, G. H. Barlow,[3] that Bright was probably the most outstanding. Barlow felt that Bright had contributed much to the advancement of knowledge of particular diseases, that he was instrumental in revolutionizing the habits of clinical teaching, and that, especially, he improved methods of investigation in pathologic anatomy and consequently helped to augment knowledge of the etiology of disease.

Richard Bright was born at Queen's Square, in Bristol, on Sept. 28, 1789. He was the third son of Richard Bright, a merchant and banker, who, it is evident, realized the benefits his son might derive from a broad and enlightened education. In 1808, Bright entered the University of Edinburgh, where he studied the arts, and in 1809 he enrolled in the medical school and studied under Hope, Munroe, and Duncan. During the summer of 1810, Bright was invited, along with Henry Holland, to accompany Sir George Mackenzie, the mineralogist, on a voyage to Iceland.

From Mayo Clinic, Emeritus Member, Section of Medicine (Dr. Keith) and Librarian (Mr. Keys).

* References 1 and 2.

His powers of observation were no doubt sharpened by this trip, for he contributed the chapters on botany and zoology to the published account of the journey, edited by Mackenzie.[4]

After Bright returned from Iceland he studied medicine in London, taking quarters in the home of one of the resident officers of Guy's Hospital. Here he studied anatomy and surgery under Astley Cooper and medicine under Babington and Currie. Doubtless Cooper stressed the importance of pathologic anatomy in the study of disease. Even at that early date, Bright made a drawing of a kidney † which revealed evidence of the disease that subsequently was to bear his name.

RICHARD BRIGHT, M.D.

Fig. 1.—Richard Bright, M.D. From a water-color drawing in the possession of his grandson Mr. R. Wallace. Reproduced in Thayer, W. S.: Richard Bright, *Guy's Hosp. Rep.* **77:** 260, 1927.

In 1812 Bright returned to Edinburgh, where he was graduated doctor of medicine in September, 1813. After two terms at Cambridge he returned to London, where he studied diseases of the skin under Bateman (Fig. 1).

Bright then took a long holiday, a traveling tour of the continent, incidentally attending lectures and clinics at Vienna and Berlin. He spent the winter of 1814-1815 in Vienna. In the spring he traveled through Hungary. In the summer he returned to Brussels and then went back to London. The results of his travels were published in an impressive volume, with many superb illustrations by Bright himself [7] (Fig. 2). Garrison [8] considered Richard Bright's record of his journey from Vienna through Lower Hungary as the most important book of travels written by a physician.

† References 5 and 6.

Bright was admitted to the Royal College of Physicians in December, 1816. He then became assistant physician to the London Fever Hospital. Here he contracted a severe fever, which almost cost him his life. He began private practice in London in 1820 and, in the same year, was elected assistant physician to Guy's Hospital. In 1824 he was made full physician at Guy's, occupying the post until 1843, when he was made consulting physician. Bright acquired a fine private practice and became a leading consulting physician in London. In 1837, on the accession of Queen Victoria, Bright was appointed physician extraordinary to her Majesty. Among other notable patients were Macaulay and several physicians,

Fig. 2.—Engraving, made from a sketch by Richard Bright, of Budapest in 1815, in Bright, 1818.[7]

including John Snow.[10] Bright was twice married. He died rather unexpectedly, on Dec. 16, 1858. The symptoms before death had led to the supposition that the kidneys were affected with granular disease, but, in the report of necropsy,[11] it was said that although the right kidney contained two or three small serous cysts otherwise these organs were healthy. Death, rather, was attributable to pronounced calcareous aortic stenosis: "The aortic valves were replaced by a ring of bony matter, which closed the cavity of the artery entirely, except by a small longitudinal slit."

In addition to Bright's disease, which we shall consider at some length, as early as 1833 Bright had described pancreatic diabetes and pancreatic steatorrhoea.[12] He also is credited with an early account of acute yellow atrophy of the liver[13];

the first description in the medical literature of a case of "Addison's" disease with caseated adrenals ‡; an account of unilateral convulsions, later to be called Jacksonian epilepsy §; and acute Hodgkin's disease.[16] In Volume 2 of Bright's "Reports of Medical Cases," published in 1831, are some interesting observations of diseases of the brain and nervous system.‖ Bright and Addison's "Elements of the Practice of Medicine" contains an excellent description of acute and chronic appendicitis.[17]

During the medical career of one of us (N. M. K.) renal disease has been of continued interest. Naturally, the contributions of the great pioneer, Richard Bright, were repeatedly studied, but they have become particularly intriguing in the last few years. Two evident reasons for further study were the renewed interest manifested by many physicians in the natural course of diseases of the kidney and the fact that the one of us who is a physician became possessed of more leisure to peruse the writings of Bright. Thayer,¶ in 1927, at the celebration of the centenary of the discovery of Bright's disease, reviewed Bright's life and observations and pointed out the importance of his first volume of medical reports, published in 1827,[20] which included the famous clinical and pathologic descriptions of renal disease. This volume was a remarkable contribution to medicine and compared favorably with the observations of Laennec, who had recently died.

During the next 20 years, Bright and his co-workers published epoch-making papers on renal disease, and many of their original observations are pertinent to this day. We were fortunate last summer (1953) through the assistance of G. A. R. Winston Wills, Librarian of Guy's Hospital, in uncovering what we believe is a unique contribution of one of Bright's associates, Joseph Toynbee, to the pathologic histology of the kidney.[21] Toynbee's histologic reproductions of the normal kidney are surprisingly similar to those of his contemporary, Bowman,[22] but he added reproductions of pathologic changes in the nephron that anticipated the notable preparations, in our time, of Oliver.[23]

Bright's initial, fundamental contribution to the problem of renal disease was the correlation of three basic phenomena, the existence of which he demonstrated in certain cases. These were the presence of dropsy, an abnormal secretion of albuminous urine, and depictable pathologic changes in the kidney. His contribution combined clinical observation, the use of a scientific test,# and a study of altered anatomic structure. Bright's ability as an amateur artist gave his original drawings of diseased kidneys an important place in his publications. The colored plates of 1827,[20] depicting gross changes in the kidney, are unique and accurate. Figure 3 affords a classic picture of a diffusely granular kidney; the granular detail and coloring are especially realistic.

From differences in form and detail of the gross kidneys in 17 cases, he went on to describe three distinct forms. The first, shown in Figure 4, suggests a nonvascular kidney with degeneration and perhaps nephrosis. It is of interest that 100

‡ Reference 14, pp. 247-248.

§ Reference 14, p. 514, and Reference 15.

‖ Reference 14, pp. 247-248.

¶ References 18 and 19.

Bright's test for detection of albumin in the urine: Urine was placed in an iron spoon and the tip of it placed over a candle. If albumin was present the water (urine) became opaque and white streaks of it passed backward into the fluid.[24]

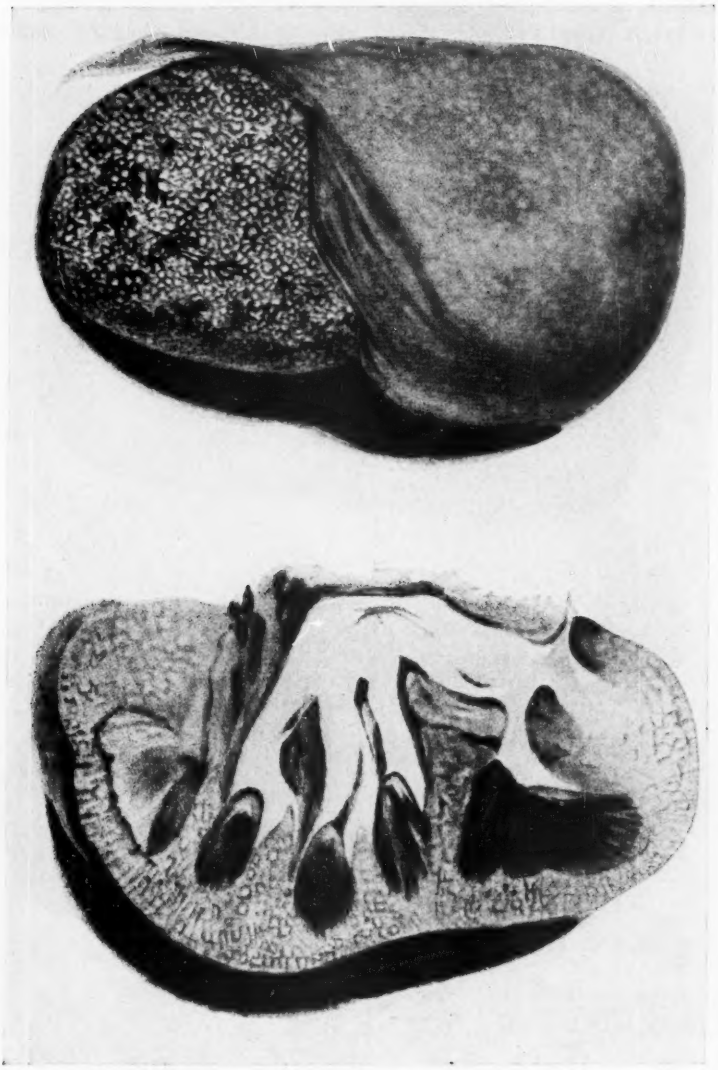

Fig. 3.—Advanced stage of granulated kidney, case of John King. This is Plate I, Figs. 1 and 2, from Bright,[20] as reproduced by Osman, A. A.: Original Papers of Richard Bright on Renal Disease, London, Oxford University Press, 1937.

years later Osman [25] was able to demonstrate amyloidosis in histologic sections of the same kidney (Fig. 5). The second form was the large white mildly granular kidney, more like an example of modern subacute or early chronic glomerulonephritis (Fig. 6). It seems that Bright included in his second group, for reasons that are not clear, a typical example of acute glomerulonephritis (Fig. 7). The third

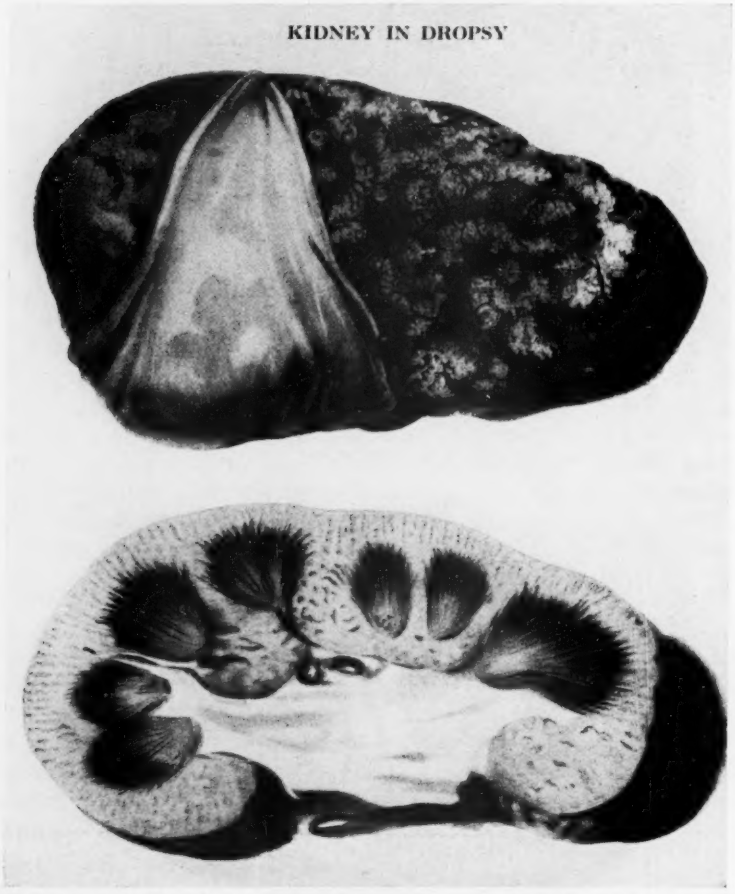

Fig. 4.—Degeneration of kidney, case of Mary Sallaway. This is Plate II, Figs. 1 and 2, from Bright,[20] as reproduced by Osman, A. A.: Original Papers of Richard Bright on Renal Disease, London, Oxford University Press, 1937. See also Fig. 5.

form, and the most readily recognized by members of the present generation, was an example of the small, contracted kidney of long-standing chronic glomerulonephritis (Fig. 8).

In 1836 Bright reviewed the findings, both clinical and pathologic, in 100 cases of renal disease.* In this, and in all of his studies, one is impressed by the

* References 26 and 27.

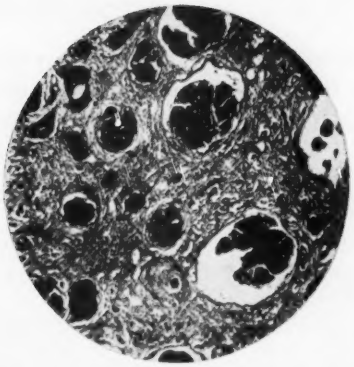

Fig. 5.—A perfect example of amyloid disease, case of Mary Sallaway. This is Museum Specimen No. 1606, microscopic section stained with methyl violet, from Osman, A. A.: Original Papers of Richard Bright on Renal Disease, London, Oxford University Press, 1937, p. 168 of appendix.

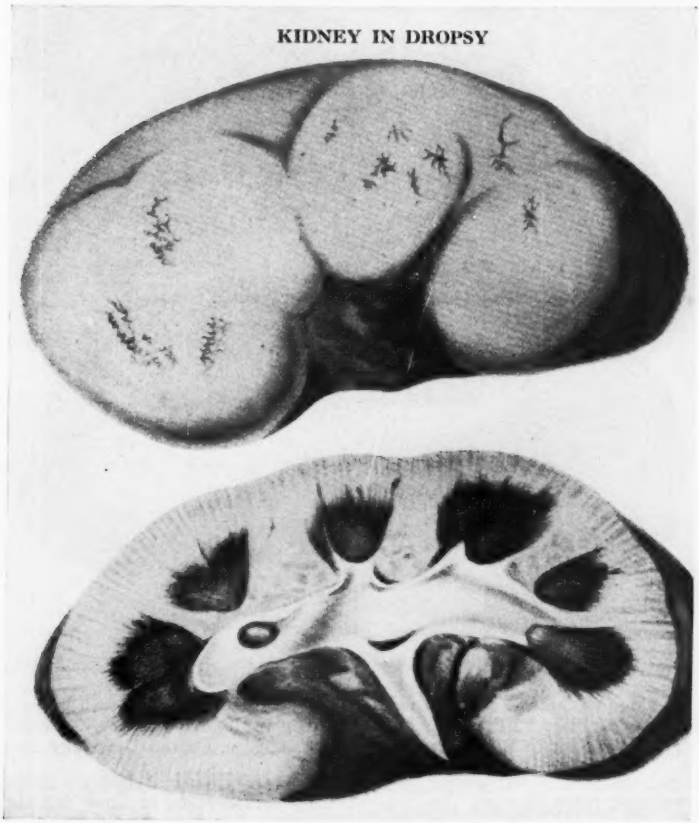

Fig. 6.—Large white kidney, case of Izod. This is Plate IV, Figs. 1 and 2, from Bright,[20] as reproduced by Osman, A. A.: Original Papers of Richard Bright on Renal Disease, London, Oxford University Press, 1937.

quantity of material assembled and the great detail in which his observations were made. He revealed that in 22 of these 100 cases the heart was grossly enlarged, because of marked hypertrophy of the left ventricle. The enlargement had occurred without any evidence of local disease of the heart or great vessels.[27] This observation led him to state in one sentence, which has since been repeatedly quoted

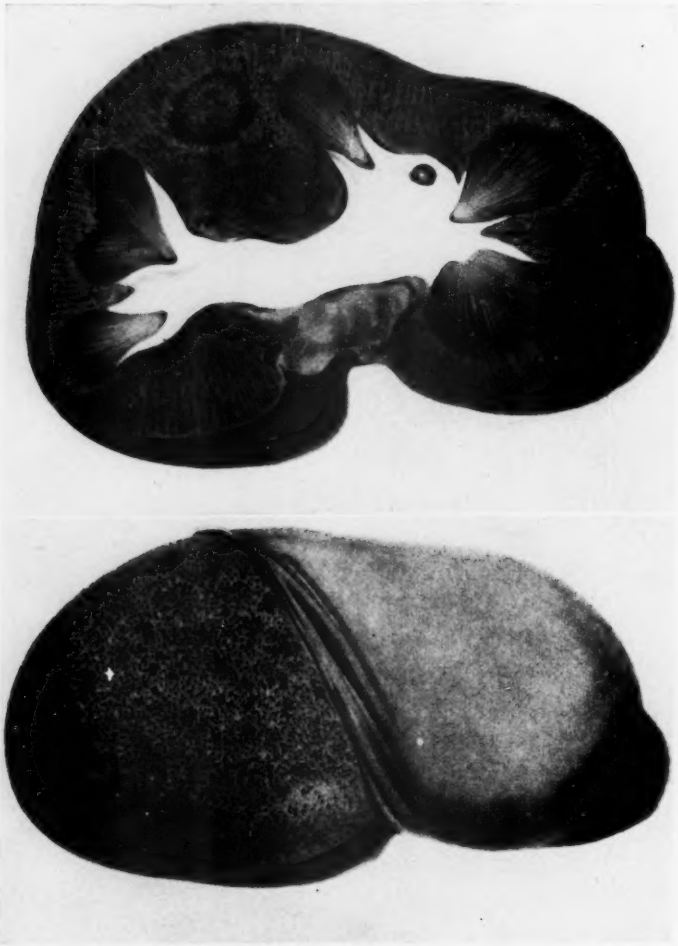

Fig. 7.—Large red kidney, acute glomerulonephritis, not recognized as such by Bright, case of Evans. This is Plate V, Figs. 1 and 2, from Bright,[20] as reproduced by Osman, A. A.: Original Papers of Richard Bright on Renal Disease, London, Oxford University Press, 1937.

> The two most ready solutions [for this hypertrophy] appear to be either that the altered quality of the blood affords irregular and unwanted stimulus to the organ immediately; or that it so affects the minute and capillary circulation as to render greater action necessary to force the blood through the distant subdivisions of the vascular system.

Thus, from an observation in gross anatomy Bright added hypertension, an abnormal physiologic condition, to what already seemed to be a complex disease.

At this juncture, Bright clearly sensed the importance of introducing new scientific methods, which were at that time increasing rapidly, to the study of renal disease. Histology, for example, was revealing the intricacies of cellular structure,

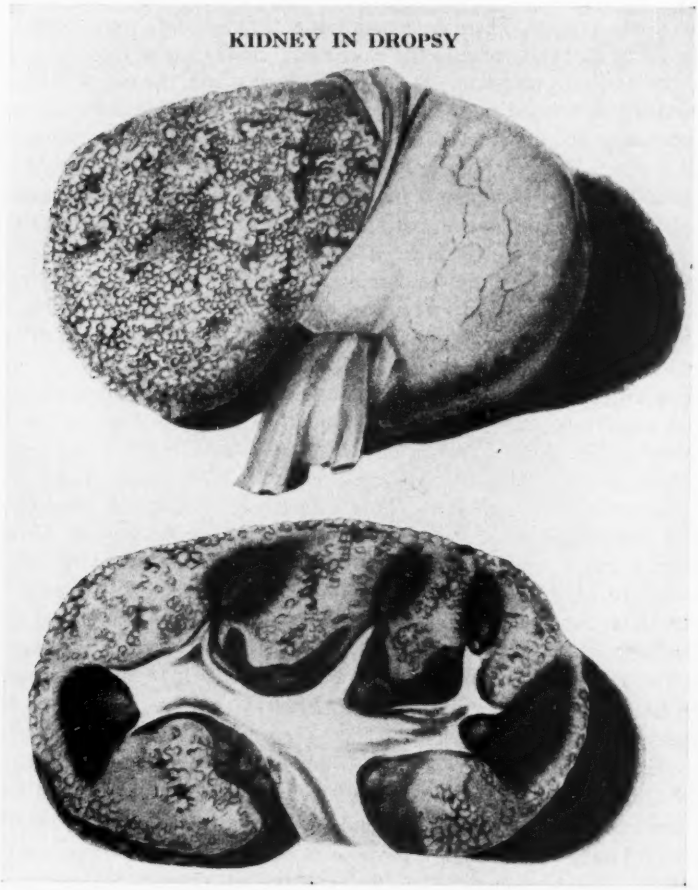

Fig. 8.—Contracted granular kidney, case of Elizabeth Stewart. This is Plate III, Figs. 1 and 2, from Bright,[20] as reproduced by Osman, A. A.: Original Papers of Richard Bright on Renal Disease, London, Oxford University Press, 1937.

and biochemistry, though still in its infancy, was laying the foundation for its later growth. Evidence of this new approach to biologic problems was the successful synthesis of urea from organic chemical substances, by Wöhler,[28] in 1828. Bright introduced some of these scientific techniques into his study of diseases of the kid-

ney. Bostock,† Babington,‡ and Rees § furnished him with important facts regarding chemical changes of the urine and blood in anasarca and in uremia. His cooperation with Toynbee led the latter to confirm Bowman's || description of the histologic features of the normal nephron and led Toynbee himself to outline the histopathologic changes of the nephron in glomerulonephritis.

As time went on, Bright realized the great variety of conditions that might arise in the course of nephritis. These included certain metabolic disorders which his associates demonstrated by chemical techniques; for instance, hypoproteinemia, lipoidemia, and uremia. These demonstrations, although data were meager, anticipated by 70 or 80 years some of the biochemical findings now thoroughly appreciated by the medical profession. The test for albuminuria, the use of which Bright so persistently advocated in cases of dropsy, soon became, and has continued to be, a necessary accompaniment of routine medical examination throughout the world.

In 1842 Bright wrote a significant letter to the *London Medical Gazette*.[31] He informed the medical profession that his associate, Toynbee, had made microscopic studies of sections of minutely injected kidneys, obtained in a large series of cases of renal disease, and that publication of the results, including engravings, soon would follow. Incidentally, Bright added that one of the most interesting features of the study was the various changes that the corpora malpighiana suffer, from the onset till the terminal stage of the disease.[31]

Joseph Toynbee (Fig. 9), to whom Bright referred in his letter, was to become a famous aural surgeon.[32] Born in 1815, at Heckington, in Lincolnshire, he was apprenticed to Mr. William Wade, of the Westminster General Dispensary, Soho. He studied anatomy with Mr. George Derby Dermott at the Little Windmill Street School of Medicine. Here, Toynbee's careful dissections were of especial benefit in preparing him for a lifetime of dissection of the human ear. He attended St. George's and University College Hospitals and was admitted to membership in the College of Surgeons of England in 1838. In 1839, Toynbee injected a granular kidney and noticed that the blood vessels of the Malpighian tuft were considerably enlarged. He showed Bright several additional specimens which he had used to illustrate this phenomenon. From 1840 to 1844, Toynbee and Bright injected nearly 100 kidneys. In 1841, at Bright's expense, a series of drawings and engravings was made. Bright, as Toynbee acknowledged, was of great assistance to him. Indeed, one of Toynbee's fundamental papers, "Pathological and Surgical Observations on the Diseases of the Ear," was communicated by Bright at the meeting of the Royal Medical and Chirurgical Society [33] on June 21, 1841. As D'Arcy Power has written,[34] Toynbee raised aural surgery from the status of

† Cited by Bright.[20]

‡ Cited by Bright.[26]

§ References 29 and 30.

|| Sir William Bowman, 1816-1892. In 1842, Bowman, as mentioned by F. H. Garrison (An Introduction to the History of Medicine: With Medical Chronology, Suggestions for Study and Bibliographic Data, Ed. 4, Philadelphia, W. B. Saunders Company, 1929, p. 472), stated his theory of urinary secretion. He believed that the renal tubes and their capillaries are most likely concerned in the secretion of the basic substances of the urine and that the function of the Malpighian bodies is to separate from the blood the watery portion.[22] Bowman, who made many contributions to physiology, was also an outstanding ophthalmic surgeon.

quackery to a legitimate branch of surgery. Joseph Toynbee died on July 7, 1866, from the accidental inhalation of chloroform with which he was making experiments to alleviate the intense pain brought about by inflammatory conditions of the middle ear. Arnold Toynbee (1852-1883), the social philosopher and economist, was the second son of Joseph, and Joseph's grandson is Arnold Toynbee, the prominent historian.

In the *Philosophical Transactions of the Royal Society,* in 1842, appeared Bowman's celebrated article,[22] "On the Structure and Use of the Malpighian Bodies of the Kidney with Observations on the Circulation Through That Gland." His drawings of the normal glomeruli of several animals, including the frog, snake,

Fig. 9.—Joseph Toynbee, from "A History of Oto-Laryngology," by R. Scott Stevenson and Douglas Guthrie, Edinburgh, E. & S. Livingstone, 1949.

guinea pig, rabbit, horse, and man, would enhance any modern textbook of histology. The drawing reproduced in Figure 10, representing the plan of the renal circulation in mammalia, was accurately copied from preparations of the human kidney. Bowman stated that each glomerulus is situated at the extremity of a renal tubule, and he expressed the belief that its function is to separate from the blood the watery portion. Bowman, and subsequently Toynbee, agreed that there is a glomerulus at the beginning of each tubule, but they disagreed as to the precise nature of the communication between glomerulus and tubule—an honest difference in the interpretation of their data, we should say, when the limited knowledge of physical chemistry in their day is considered.

Toynbee's article, the content of which was mentioned by Bright in his letter of 1842, appeared in the *Transactions of the Medical and Chirurgical Society of London* in 1846. It was entitled "On the Intimate Structure of the Human Kidney and on the Changes Which its Several Component Parts Undergo in 'Bright's Disease.'" [21] His technique included injection of colored material into both the arterial and tubular systems (the latter via the ureter) and preparation of histologic sections for microscopic examination. That he had a good grasp of the intimate structure of the normal kidney is evident from Figure 11, which shows the distribution of the nephrons in a portion of the cortex and pyramid. His drawings of the pathologic alterations in Bright's disease disclose an uncanny knowledge of the changes in the individual nephron. They depict the following: enlarged glomeruli, evident in Figure 12, right; diseased blood vessels within the interior of the glomerular capsule, shown in Figure 13, left, and tubules that are dilated in one

Fig. 10.—Plan of renal circulation in mammalia: × 40. This is Figure 16 from Bowman,[22] read Feb. 17, 1842.

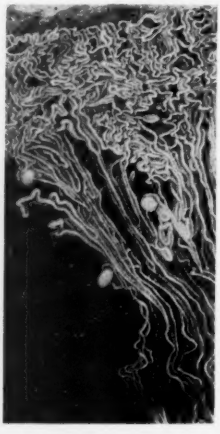

Fig. 11.—Distribution of nephrons in a portion of cortex and pyramid of normal human kidney. This is Plate VII, Fig. 1, from Toynbee,[21] read June 23, 1846.

portion and constricted in another, reproduced in Figure 13, right. Toynbee concluded that there are three stages of Bright's disease: (1) an acute phase with an enlarged, swollen kidney and noticeably hypertrophied glomeruli, (2) a later stage, in which the kidney is enlarged and has a smooth surface and there are alterations in the glomerular capsules and tubules, including dilatation and constriction, and (3) a third stage, in which there is a small firm granular kidney. In this kidney the arteries generally, and the vessels within the glomeruli, were injected with difficulty. The capsules of some glomeruli were contracted, and groups of tubules were clumped into rounded masses on the surface of the kidney; many tubules were difficult to inject, and dilatation and constriction were of frequent occurrence.

Toynbee's work has a fundamental ring to it. His engravings remind one of some of Oliver's reproductions of diseased nephrons, which the latter obtained by techniques distinctly different from those of Toynbee. Oliver's book, "Architec-

ture of the Kidney in Chronic Bright's Disease," was published in 1939,[23] 93 years after Toynbee's paper. See Figure 13, left and right (Toynbee) and Figure 14, left and right (Oliver).

With this broad background of knowledge regarding what we now term "glomerulonephritis," Bright instituted, in 1842, one of the early attempts to add intensive clinical investigation to the study of disease. He obtained permission from the authorities of Guy's Hospital to observe and study clinical cases of nephritis in two hospital wards for a period of six months. The arrangements included a nearby history room and small laboratory. To man the latter, Bright chose Rees, a clinical pathologist. The results of this work are recorded in the hospital reports of 1843.¶ The plan of reporting is a familiar one today. Two

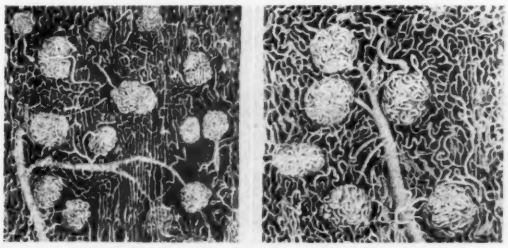

Fig. 12.—Left, healthy Malphighian bodies. This is Plate IX, Fig. 1, from Toynbee.[21] Right, diseased, hypertrophied Malpighian bodies and dilated vessels. This is Plate IX, Fig. 2, from Toynbee.[21]

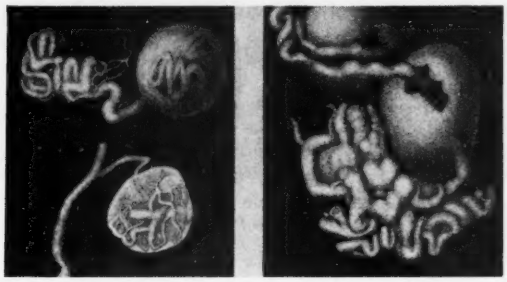

Fig. 13.—Left, diseased blood vessels in the interior of the Malpighian capsule. This is Plate X, Fig. 2, from Toynbee.[21] Right, tortuous and varicose tubuli uriniferi. This is Plate XI, Fig. 3, from Toynbee.[21] A footnote in Toynbee,[21] p. 326, reads as follows:

"In conducting the researches from which all of the above engravings were taken, Powell's ½ inch object glass was used, the magnifying power of which is about 80 diamaters."

tables are appended, one detailing historical and clinical data, the other, certain chemical findings relative to the blood and urine. Then follow pathologic reports and realistic reproductions of gross renal changes. New discoveries listed in the report were (1) the demonstration of wide diffusion of urea throughout the fluids of the body when severe renal insufficiency exists and (2) the not frequent presence of hydremia.

As time passed, Bright and his co-workers became interested in the ultimate course of glomerulonephritis. It often happens that the pioneer studies of a new

¶ References 30 and 35.

disease are made on patients who have reached an advanced or terminal stage. This was the experience of the group at Guy's Hospital, and it led them to a pessimistic prognosis. However, after a decade of observation, Bright,[36] Barlow,[37] and others realized that there were acute cases in which recovery took place, and modern statistical studies of such cases have revealed that cure is permanent in 80 or 90%. The group at Guy's Hospital also stressed the possible relationship between exposure to cold and the onset of acute nephritis. The symptoms and signs, however, usually have been interpreted as indicative of the onset of an infectious process. Nevertheless, the fact that exposure to cold can cause shock-like symptoms in the absence of infection lends support to the conception that factors other than invading microorganisms must be considered etiologic. Bright also learned that, in some cases, the chronic types of disease were arrested and the patient lived comfortably for several years. Similar cases are now more frequently noted, and even recovery from chronic glomerulonephritis has been reported. An interesting prognostic

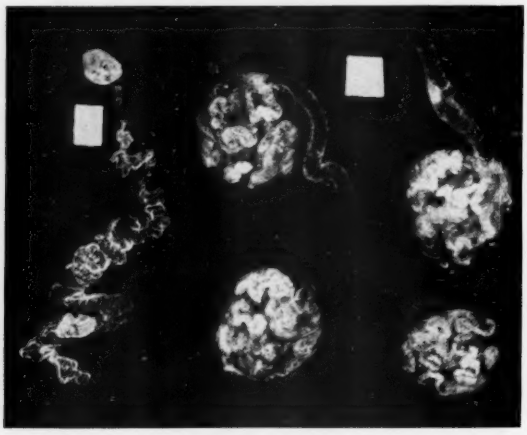

Fig. 14.—Left, a glomerulus and a portion of the proximal convolution, greatly dilated and showing a marked fatty change in its thin, translucent wall; × 15. This is Plate II, 13, from Oliver,[23] p. 201. The tissue represented was from case XXXVI Verna G., in Addis, T., and Oliver, J.: The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931, pp. 343-347. Compare with Figure 13, right. Right, detail of glomeruli showing fatty deposits in the vascular tufts. The tufts are swollen and their lobulation distorted or obliterated; × 80. This is Plate II, 15, from Oliver,[23] p. 201. The tissue represented was from case XXII Frederick B., in Addis and Oliver, pp. 278-282. Compare with Figure 13, left. The microscopic procedure for both parts of this figure consisted of (1) tearing out of tissue after maceration in concentrated HCl and (2) camera lucida drawings of tissue in distilled water viewed with a binocular microscope (Oliver,[23] pp. 3 and 4).

error made by Bright was related by Hawkins.[38] In 1849 Bright was consulted by a physician 45 years of age, who had pronounced and persistent albuminuria. Bright is said to have expressed the opinion that the patient could not live for more than two years. He lived comfortably, however, and the albuminuria persisted for 43 years; the patient died of cerebral hemorrhage at the age of 88.

What manner of man was Bright? His contemporaries mentioned his modesty, directness, and magnanimity. His relations with others, and this includes his medical confreres and patients, were cordial. For example, when he was studying nephritis intensively, patients who had the disease, and were on the services of

his medical associates, frequently were transferred, at their suggestion, to his ward. That he was socially minded is indicated by his frequent references to the meager economic resources of his hospital patients and to injustices inflicted on the peasants in the countries in which he traveled. He gave little evidence of personal conceit, and his equanimity under stress frequently has been mentioned. It is evident that he was capable of admitting mistakes and of learning from them.

Bright possessed a gifted and balanced mind. His contemporaries repeatedly mentioned a singular power of observation, combined with clear judgment and independence of thought. His research studies included excellent controls; these applied especially to investigations of the urine and blood and to his work in morbid anatomy. Bright had a keen sense of what he believed to be true, and his philosophic discussions of his discoveries are thorough and to the point. He purposely minimized theoretical considerations. It is significant, we think, that Bright inspired young investigators and instructed them in the ways of research.

What then were the lasting contributions of Bright and his school to renal disease? Twenty years of thorough and persistent study revealed to them a disease that was diffuse, involving many tissues; often there was a specific renal lesion, and the prognosis in chronic cases was poor. Bright insisted that there were four important interrelationships in the disease and gave abundant evidence of their occurrence. These were the presence of edema, cardiovascular alterations, certain abnormal metabolic disturbances, and renal dysfunction. These four phenomena, the tetralogy of Bright, are still basic facts. Modern investigators of glomerulonephritis have advanced knowledge of the disease by physiologic, biochemical, bacteriologic, and pathologic investigations based largely on the phases first described by Bright 127 years ago.

Certain contributions of Bright to renal disease require further elaboration. Students of the problem realize how vital some of them are today and concur with Wilks # that Bright himself did not always grasp their significance. The majority of his reported cases of renal disease, 160 in all, were examples of diffuse glomerulonephritis,[40] but he did include, in his series, cases of chronic lipoid nephrosis and cases of diffuse arteriolar disease with hypertension. These latter two groups were subsequently described by others as representative of distinct syndromes, to be distinguished from glomerulonephritis. In contrast to this subdivision of Bright's original series of cases, there is at present a tendency to consolidate them again in a single group. This comprehensive viewpoint suggests the possibility of common denominators in the numerous types of cardiovascular renal disease. A similar idea was expressed by Mahomed in 1881, when he termed essential hypertension "Bright's disease without albuminuria" [42] and when Volhard [43] and others,* from 1918 to 1926, stressed certain common patterns in the development and course of eclamptic toxemia. This wider conception of vascular renal disease is worthy of further investigation.

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BEHAVIOR OF SERUM IRON IN VARIOUS DISEASES OF LIVER

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SINCE the liver is the body's chief repository of stored iron, it was inevitable that clinical investigation of the organ in its diseased state eventually included disturbances in that function of storage. Widespread use of needle biopsy has led to the realization that siderosis of the liver not infrequently follows acute viral hepatitis and certain nutritional disturbances.[1] In turn, that observation has stimulated the investigation of changes in serum iron resulting from hepatic disease, particularly viral hepatitis. Reports of such studies are common in European literature but are few in this country, a real oversight when one considers the conclusion drawn by one investigator that "acute hepatitis is the only disease in human beings which is consistently associated with a marked hypersideremia." [2] The conclusion indicates a remarkable degree of specificity which, unfortunately, cannot often be assigned to a laboratory procedure. Certainly, it warrants investigation of serum iron determination as a test of hepatic function in the differential diagnosis of jaundice—still a problem in spite of the aids already at the disposal of the clinician, including extensive hepatograms and needle biopsy.

The purpose of this paper is to describe the behavior of serum iron in various diseases of the liver and to present an evaluation of its determination in the differential diagnosis of hepatic disease, particularly that associated with jaundice.

MATERIAL

Conclusions drawn from this study are based, for the most part, upon 659 serum iron determinations in 313 subjects. Of the latter, 50 were normal persons selected from the pool of hospital employes, 28 were patients without evidence of liver disease, 27 were patients with abnormal liver-function tests due to undetermined causes, and 15 were employees initially selected as normal subjects but subsequently excluded from that group when they were found to have abnormal survey liver-function tests. The remaining 193 persons were patients with liver disease, the exact nature of which was established in most instances by means of needle biopsy, laparotomy, or autopsy. A few diagnoses were made by virtue of history, physical examination, and laboratory findings when there was no doubt as to the nature of the disease. All but 13 of the patients were from the medical and surgical services of the Veterans Hospital, in New Orleans. The other 13 were from neighboring institutions and medical practices within one-day mail service of New Orleans.

METHOD

Serum iron was determined by the method of Schales,* which is essentially the method of Barkan and Walker.[4] Four milliliters of serum was mixed with 2.0 ml. of 0.3 N hydrochloric acid and allowed to stand for an hour. Then, with constant agitation, 2.0 ml. of 20% trichloroacetic acid was added; the mixture was allowed to stand for 10 minutes (or until separation occurred)

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* Cited in Reference 3.

and then was centrifuged for 30 minutes at 3,000 rpm. Four milliliters of the supernatant fluid was placed in a 19 by 105 mm. Coleman cuvette (matched cuvettes were used throughout the study), to which were added the following reagents in the order given: 0.2 ml. of 50% ammonium acetate solution; 0.3 ml. of 1% hydroquinone solution; 1.0 ml. of 0.1% orthophenanthroline solution. After an hour the per cent transmittance was determined by reading in a Coleman Junior Spectrophotometer, Model *6A*, at 500 mμ. The quantity of iron was expressed in micrograms per 100 ml. of serum after comparison with a series of standard iron solutions treated in a like manner. Included in each group of unknown sera were a blank (to check reagents and glassware for iron contamination) and three standard iron solutions (to check reliability of reagents and technique).

The color-complex formed between orthophenanthroline and ferrous iron is stable once adequate time has been allowed for it to develop;[5] 20 minutes are sufficient in most instances, but in this study an hour was allowed. Results using the method are reproducible. That important prerequisite was proved to our satisfaction by the running of duplicate determinations on 50 sera selected at random. Since the transport iron is but a small fraction of the total iron present in whole blood, a question arises relative to the effect of hemolysis upon serum iron values. When the aforementioned method is used, the effect of slight hemolysis is negligible.[4] To determine the effect of hemolysis of various degrees, the following study was conducted: Specimens of blood were obtained from 50 persons, and the serum iron was determined in each. Then to each serum was added a carefully measured quantity of iron derived from its respective hemoglobin, which had been lysed in distilled water. After the addition of hemoglobin iron, the serum iron was again determined. It was found that when the quantity of hemoglobin iron thus added exceeded 1.0 mg. per 100 ml. of serum the serum iron value was invariably increased. However, when the quantity added was less than 1.0 mg. per 100 ml. of serum effect on the serum iron level was variable; i. e., it was increased in some instances and decreased in others. Such variability suggests that under conditions of the method some free hemoglobin has an affinity for ionic iron, while other free hemoglobin does not. This intriguing observation was not explored further. It was concluded that serum exhibiting visible hemolysis was unfit for iron determination; accordingly, all such sera were eliminated from this study.

Throughout the study iron determinations were made on specimens of serum obtained from subjects in the morning while they were in the fasting state. Exceptions were a few of the 13 specimens received from outside the Veterans Administration Hospital. The purpose of that rule was to maintain as a constant the normal, unexplained diurnal variation of the serum iron which may result in morning values (actually, the values after a period of rest) being as much as 30% higher than values determined later in the same day.[6] Only through such careful attention to the time of blood-letting can interpretations of abnormally high serum iron values become meaningful.[7]

An effort was made to run the following liver-function tests on each specimen of serum analyzed for iron content: total bilirubin, thymol turbidity, gamma globulin, lipid turbidity, and cephalin flocculation; cholesterol partition was done on selected sera. Patients with liver disease, moreover, had complete "batteries" performed, which included, in addition to the aforementioned tests, the following: total protein with albumin-globulin ratio, prothrombin time, sulfobromophthalein (Bromsulfalein) retention, urine urobilinogen, and (when indicated) fecal urobilinogen.

RESULTS

Over-all results of the study are presented graphically in Chart 1, which shows the distribution of serum iron values in normal persons and in those with a variety of liver diseases. Only the highest value found in each person contributed to the mean determined for any particular group.

A. Establishment of Normal Mean.—Fifty hospital employees were selected who met the following criteria of normality: (1) no iron intake other than normal dietary content, (2) no blood loss other than normal menses during the preceding six months, (3) no history of liver disease, (4) no intercurrent infection, and (5) no abnormality of survey liver-function tests. Among the 50 chosen there were 19

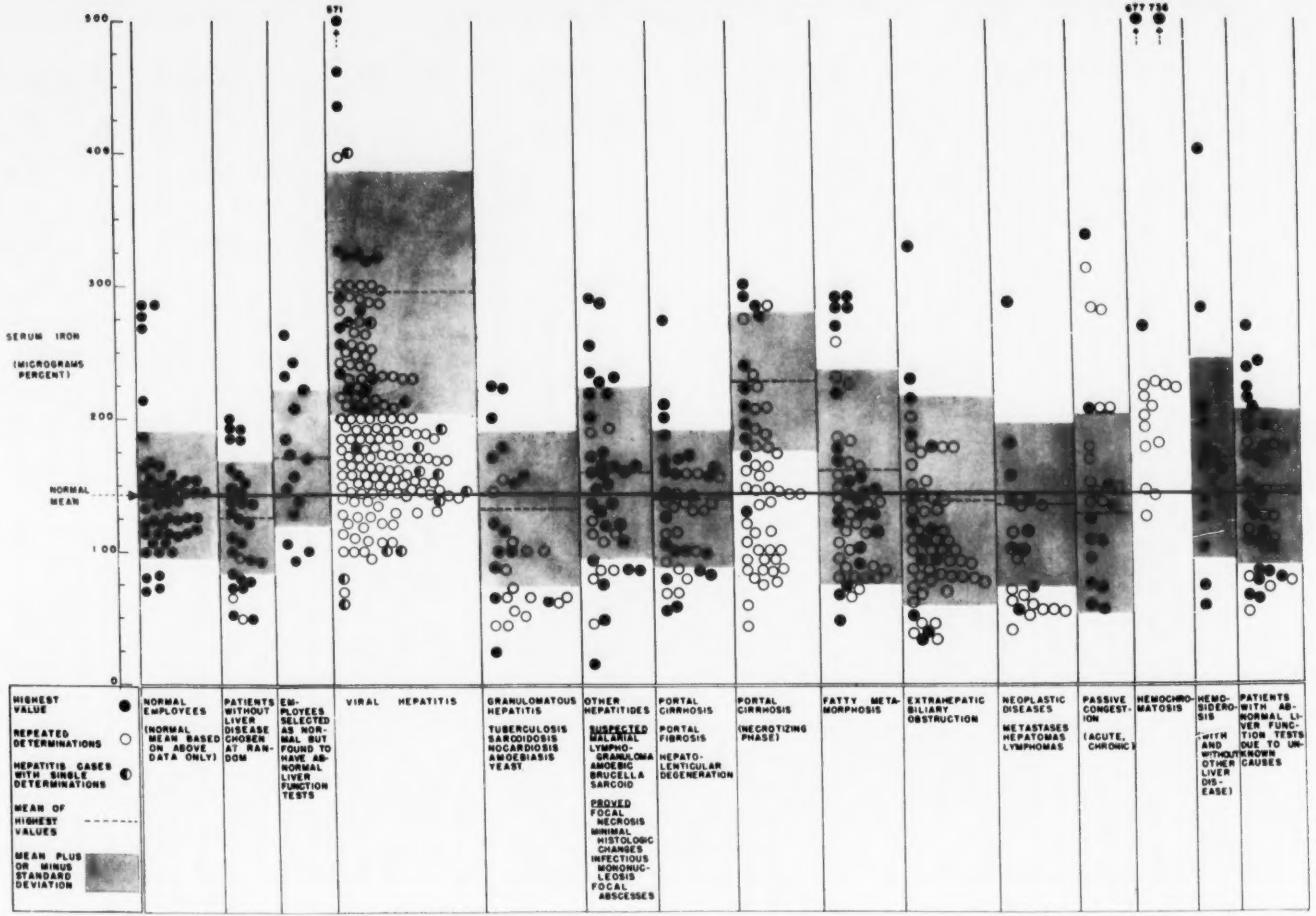

Chart 1.—Results of 659 serum iron determinations in 313 subjects in various hepatic states.

white men (with a mean of 166 γ per 100 ml.), 18 white women (with a mean of 125 γ per 100 ml.), and 13 Negro men (with a mean of 135 γ per 100 ml.). The mean serum iron of the entire group, and that figure hereinafter referred to as the normal mean, was 143 γ per 100 ml., with a range from 70 to 286 γ per 100 ml. The occasional high values found in persons meeting the rigid criteria of normality established for this study argue for caution in assigning clinical significance to a single high value found in a patient, particularly if that value is less than 300 γ per 100 ml. The normal mean, of 143 γ per 100 ml., is exactly the figure quoted by Lichtman [8] and is essentially the figure quoted by Lemberg and Legge [9]; it is slightly higher than the value determined by Peterson [2] and is significantly higher than the value determined by Matassarin and Delp.[10]

In selecting the group of 50 normal subjects there were encountered 15 apparently healthy persons who had to be rejected because of abnormalities in survey liver-function tests. The mean serum iron of that group was 171 γ per 100 ml. There was no ready explanation for those abnormalities. Some of the subjects were restudied at a later date and found to be normal; however, they were not added to the group whose data supplied the normal mean. For the benefit of comparison, serum iron was determined in 28 patients who had no evidence of liver disease; the mean value established in that group was 126 γ per 100 ml.

B. Serum Iron in Viral Hepatitis.—There were 33 patients in this group; 20 had serial iron determinations, and 13, those outside the Veterans Administration Hospital, had single determinations. Only the highest value in each of our own 20 patients, or those who were known to have met without doubt certain criteria for the diagnosis of viral hepatitis, was used in establishing the mean serum iron level of the group. That figure was 297 γ per 100 ml., with a range from 178 to 571 γ per 100 ml. The mean compares favorably with the value of 295 γ per 100 ml. established by Peterson in a group of 60 patients with acute viral hepatitis.[2] In our group with hepatitis, 32 had the infectious or endemic type and only 1 had the homologous serum type; no effort was made to keep their data separate.

Chart 2 compares the results of serial iron determinations in 6 patients with viral hepatitis, who were selected at random from the group of 20 so studied, with the findings in 6 patients with other liver diseases.

Several points are illustrated by this chart. 1. Serum iron values tend to be higher and more persistently elevated in viral hepatitis than in other representative diseases of the liver, regardless of the extent of parenchymal damage associated with the latter. 2. There is no constant correlation between the severity of viral hepatitis and the degree of serum iron elevation. Patients with mild infections may have more spectacular elevations than those with severe infections, but this is not necessarily so. 3. Although in viral hepatitis serum iron values tend to be highest when morbidity is at its peak and serum bilirubin is maximally elevated, there is no constant correlation between the serum iron and either the serum bilirubin or the clinical course of the disease. In general, the serum iron tends to return to normal as the patient with viral hepatitis recovers, but it does not do so progressively nor abruptly. Rather, the curve of serial determinations undulates in a generally downward direction until the normal range is reached. 4. A markedly elevated serum bilirubin level does not imply a similarly elevated serum iron level nor does a slightly elevated serum bilirubin level imply a similarly elevated serum iron level.

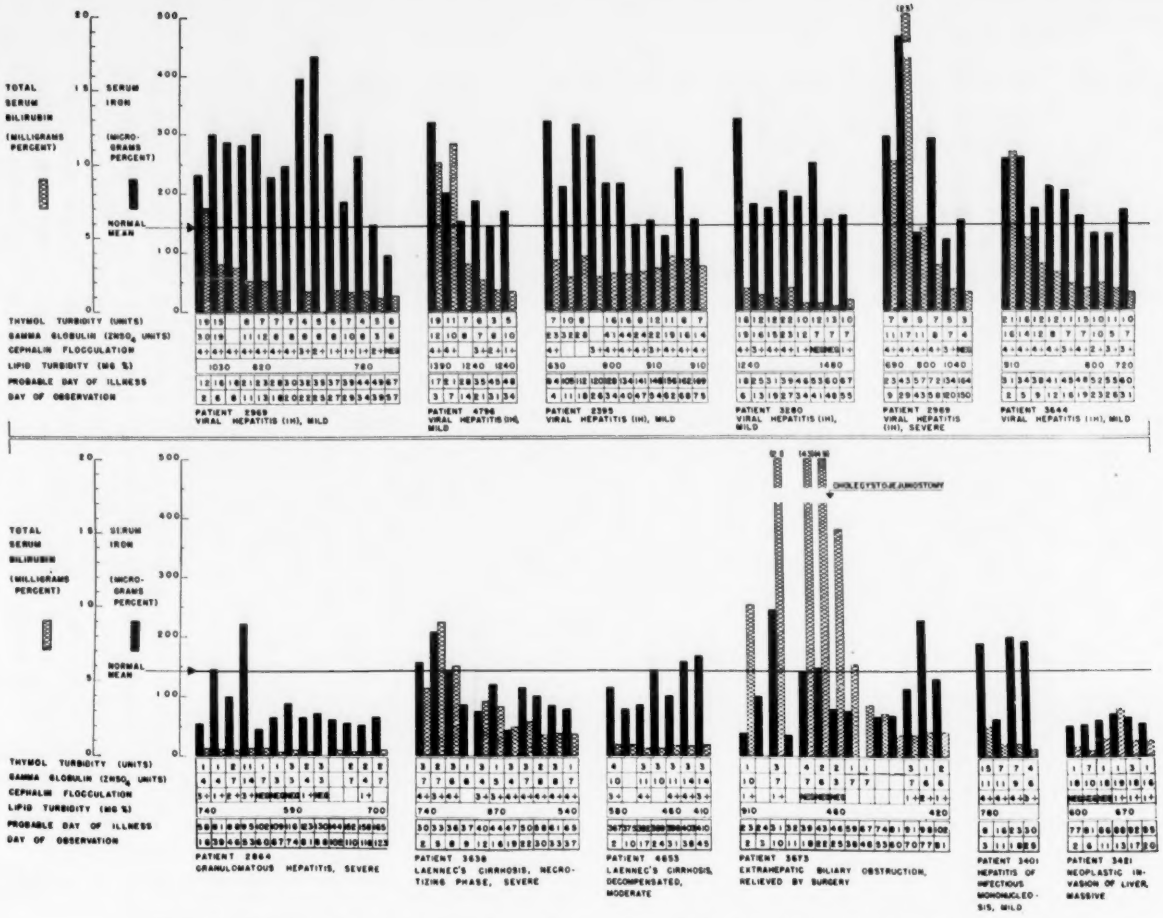

Chart 2.—Comparison between serum iron values in six patients with viral hepatitis and those in six patients with other hepatic diseases.

The value of the serum iron determination in the differential diagnosis of jaundice hinges upon those observations and is well illustrated in Chart 2 if one compares Patient 2989 with Patient 3673. Patient 2989 had severe viral hepatitis, and his serum iron level was significantly elevated when his serum bilirubin level reached its peak. Patient 3673, on the other hand, had extrahepatic biliary obstruction, and his serum iron level remained normal while his serum bilirubin level was maximally elevated, even though the amount of his bilirubin was twice that of Patient 2989. These observations suggest that in patients with jaundice who manifest evidence compatible with either intrahepatic obstruction (as in the acute phase of viral hepatitis) or extrahepatic obstruction the demonstration of a significantly elevated serum iron level is indicative of viral hepatitis as opposed to extrahepatic biliary obstruction.

Chart 3 shows the effect of duration of illness upon the serum iron level of patients with viral hepatitis. Duration of illness has been dated from the onset of prodromal symptoms rather than from the onset of jaundice. It will be noted that most of the patients were initially studied during the first three weeks of illness. About half of them sought hospitalization when they became ill; the other half delayed hospitalization until they were alarmed by the appearance of jaundice. There is no constant correlation between the duration of illness and the serum iron level; however, a few trends are demonstrated by Chart 3. 1. During the first two weeks of viral hepatitis serum iron tends to be increased, but in the patients studied it was not increased sufficiently to support diagnostic conclusions. 2. During the third week, however, serum iron values are significantly elevated. 3. Significant increases in serum iron may be found during the fourth to eighth week of viral hepatitis. 4. Although the validity of results is open to question because of the small number of patients who can be kept in the hospital beyond eight weeks, a tendency is shown for serum iron level to return to normal between the 8th and 12th week of illness.

C. Serum Iron in Granulomatous Hepatitis.—There were 15 patients in this group, and the diagnosis was established in each by means of biopsy. The mean serum iron level was 132 γ per 100 ml. (Chart 1). Specific diagnoses included tuberculosis, sarcoidosis, nocardiosis, and amebiasis; the one patient diagnosed as having an unidentified yeast infection has since been proved to have melioidosis. Liver-function tests are of no real value in delineating granulomatous hepatitides. True, such tests may indicate the presence of disease, but definitive diagnosis must await liver biopsy, without which the diagnosis of granulomatous hepatitis is ethereal. Within the limits of that qualification, serum iron determination may be of value in differentiating between viral and granulomatous hepatitides, in which event a significantly elevated value argues for the former. Probably the most useful application of the test in this problem would occur when viral hepatitis is anicteric or when granulomatous hepatitis is associated with jaundice. However, the test is not proposed in lieu of liver biopsy when the latter is feasible.

D. Serum Iron in Other Heptatitides.—There were 31 patients in this group, and the mean serum iron level was 159 γ per 100 ml. By far, most of the diagnoses were established through liver biopsy, and they included focal necrosis, minimal histologic changes, infectious mononucleosis, and focal abscesses. Other diagnoses, based upon acceptable clinical data short of biopsy, included malaria, lymphogranu-

loma, amebiasis, brucellosis, and sarcoidosis. When Chart 1 is reviewed, it becomes apparent that several serum iron values in this group were sufficiently elevated to infringe upon the range occupied by the high values in viral hepatitis. However, the test may be of value in differentiating between viral hepatitis and these hepatitides, provided values are significantly and persistently elevated, thereby arguing for the former. In this respect, the critical level of serum iron elevation appears to be 300 γ per 100 ml. As applied in the diagnosis of granulomatous hepatitides, the test would probably be of greatest value when viral hepatitis is anicteric, or when the other hepatitides are associated with jaundice. Again, it is proposed as an adjunct

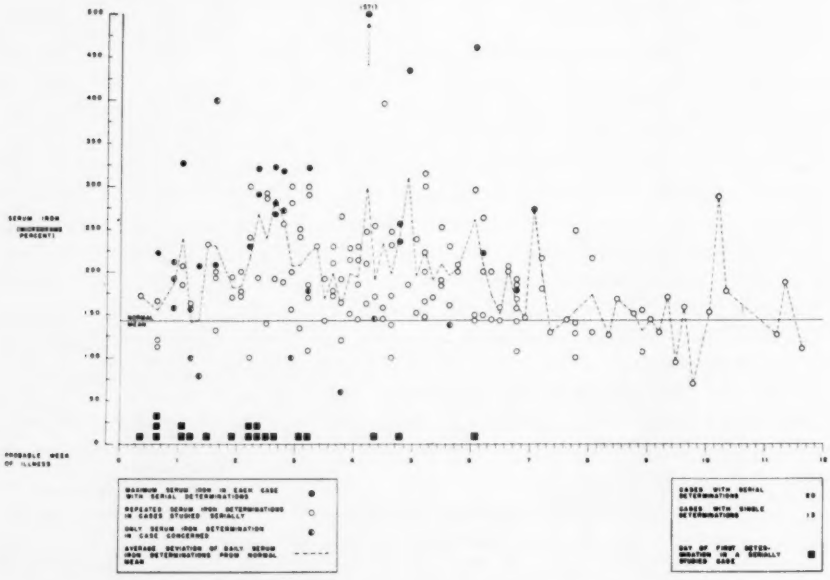

Chart 3.—Effect of duration of disease upon serum iron in viral hepatitis.

to other hepatic function tests, in comparison with which it has more specificity in this particular problem; however, liver biopsy remains the preferable procedure when it can be done.

E. Serum Iron in Portal Cirrhosis.—There were 23 patients in this group, and the mean serum iron level was 139 γ per 100 ml. Diagnoses were based upon histologic studies and included not only classic portal cirrhosis but also degrees of portal fibrosis short of actual cirrhosis; one patient had combined hepatolenticular degeneration. There is a significant disparity between the mean serum iron of this group and the mean of the hepatitis group; further, there is infrequent overlapping of the high values. It follows, then, that serum iron determination may differentiate between viral hepatitis and portal cirrhosis, significantly elevated values being indicative of the former. The test would probably be of most benefit when portal cirrhosis is associated with jaundice, for then the clinician is ofttimes hard put to differentiate between the two diseases on the basis of other clinical data short of biopsy.

In this particular problem, and in the presence of jaundice, serum iron determination would have greater specificity than other applicable function tests, but it would be, of course, less definitive than biopsy.

F. Serum Iron in the Necrotizing Phase of Portal Cirrhosis.—There were 11 patients in this group, with a mean serum iron level of 227 γ per 100 ml. In Chart 1, it is noteworthy that the mean of this group, whose liver disease so closely resembles viral hepatitis both clinically and histologically, approaches the mean of the hepatitis group more closely than does the mean of any other group studied. However, there is some evidence that serum iron determination may be even more definitive than biopsy in differentiating between these two diseases. That observation is illustrated by Patient 2989 in Chart 2. Initial biopsy, performed because of indecisiveness of function tests in conjunction with history and physical findings, presented a histologic picture indicative to some of acute viral hepatitis but indicative to others of necrotizing portal cirrhosis. Subsequent biopsies firmly established viral hepatitis as the correct diagnosis. Throughout the period of controversy significantly elevated serum iron values had already indicted vital hepatitis. It is proposed, then, that serum iron determination become an adjunct to other liver-function tests and to biopsy when this particular problem in diagnosis arises, in which event values persistently elevated above 300 γ per 100 ml. argue for viral hepatitis.

G. Serum Iron in Fatty Metamorphosis.—There were 24 patients in this group, with a mean serum iron level of 160 γ per 100 ml. They have many points in common with those in the necrotizing phase of cirrhosis. Data of the two groups have been kept separate in this study, because in our series of 350 biopsies of the liver fatty metamorphosis has been the condition most frequently associated with siderosis of the liver. Patients with fatty metamorphosis often present a problem in diagnosis, particularly when they are jaundiced and coincident prothrombin deficiency precludes liver biopsy. In that situation serum iron determination may be of value. There is a comfortable disparity between the mean of this group and the mean of the viral hepatitis group; however, there is enough overlapping of high values to curb complete reliance upon specificity of the test unless values exceed 300 γ per 100 ml., thereby being indicative of viral hepatitis.

H. Serum Iron in Extrahepatic Biliary Obstruction.—There were 14 patients in this group, with a mean serum iron level of 137 γ per 100 ml. Patients with obstruction due to any cause were included; however, those with obstruction resulting from neoplastic disease were rejected if metastases to the liver had occurred, thus introducing another factor in serum iron variation. It is in differentiating between jaundice due to viral hepatitis and that due to extrahepatic biliary obstruction that the determination of serum iron would appear to enjoy its most valuable clinical application. Such a test is sorely needed in the early phase of hepatitis, when the disease mimics extrahepatic obstruction so well and when ill-advised surgical intervention can have disastrous results. In that situation, the demonstration of a significantly elevated serum iron level, especially upon repeated determination, would be indicative of viral hepatitis. That conclusion is encouraged by comparison of data of the two groups in Chart 1, wherein it is shown that there is significant disparity between the mean values and there is infrequent overlapping of high values. The single value above 300 γ per 100 ml. in the biliary obstruction

group was found in a patient who had a well-documented episode of hemolysis during the course of his obstruction. Serum iron values before the episode had been normal, and they returned to normal shortly after the episode.

I. Serum Iron in Neoplastic Disease of the Liver.—There were 10 patients in this group, with a mean serum iron level of 100 γ per 100 ml. Specific diagnoses included hepatomas, lymphomas, and metastatic adenocarcinomas. Liver biopsy remains the ultimate procedure in the diagnosis of neoplastic disease and should supersede all function tests. Serum iron determination has no application in this group, excepting, possibly, the delineation of jaundice. However, jaundice usually appears so late in the course of neoplastic disease of the liver that physical findings are often diagnostic; if not, biopsy rarely fails to establish the diagnosis.

J. Serum Iron in Passive Congestion of Liver.—There were 12 patients in this group, with a mean serum iron level of 127 γ per 100 ml. Great increases in serum bilirubin are infrequent in patients with passive congestion of the liver, but when jaundice does occur determination of serum iron may differentiate it from the jaundice of viral hepatitis, persistent elevation above 300 γ per 100 ml. being indicative of the latter. The test is proposed in this particular problem because biopsy is shunned for fear of hemorrhage. In Chart 1 the single value above 300 γ in this group occurred in a young man who died of liver failure precipitated by general anesthesia. It is not known for certain whether the high value reflected hemolysis, that may accompany passive congestion, or the extensive parenchymal damage that was subsequently demonstrated at autopsy. Here, again, is illustrated the inadvisability of forming diagnostic conclusions based upon a single high serum iron value.

K. Serum Iron in Hemochromatosis.—There were three patients in this group —too few to warrant specific conclusions. The highest serum iron values of the entire study were found in two of the patients. It is noteworthy that values in the same individual with hemochromatosis may be very high, or moderately elevated, or even subnormal, as demonstrated by serial determinations. Factors that probably influence such variation include hemorrhage, transfusion of whole blood, intrahepatic obstruction, and progressive parenchymal necrosis.

L. Serum Iron in Siderosis of Liver (Other Than Hemochromatosis).—There were 17 patients in this group, with and without other liver disease, but they are not included in any other group presented in Chart 1. The mean serum iron level was 169 γ per 100 ml. The range of high values, from 58 to 402 γ per 100 ml., illustrates the lack of correlation between siderosis of the liver and serum iron levels. In this group the two unusually high values were found in patients in the necrotizing phase of portal cirrhosis, the condition which most closely approaches viral hepatitis in effect upon the serum iron.

M. Serum Iron in Undetermined Disease of Liver.—Included in this group were 27 patients, who in the course of their hospitalization were found to have abnormal liver-function tests, the exact causes of which were not determined through definitive measures such as biopsy. The mean serum iron was 147 γ per 100 ml.

N. Serum Iron in Hemolytic Disease.—It is regrettable that a group of patients manifesting primarily hemolytic disease were not available for inclusion in the study. Data from such persons are needed to show variation in serum iron effected

through hemolysis, for that process may be an incidental event in the course of the hepatitides, particularly viral hepatitis. However, a few patients were observed who did have episodes of hemolysis during the course of their illness. Effect upon the serum iron was found to be variable. In some there was an increase in serum iron coincident with hemolysis; in others, no effect was noted. Such variation detracts from the specificity of serum iron determination in the differential diagnosis of jaundice when hemolysis has contributed to the bilirubinemia.

O. Correlation Between Serum Iron and Other Liver-Function Tests.—As previously mentioned, an abbreviated "battery" of function tests was run on each serum subjected to analysis for iron content. Chart 4 graphically correlates the

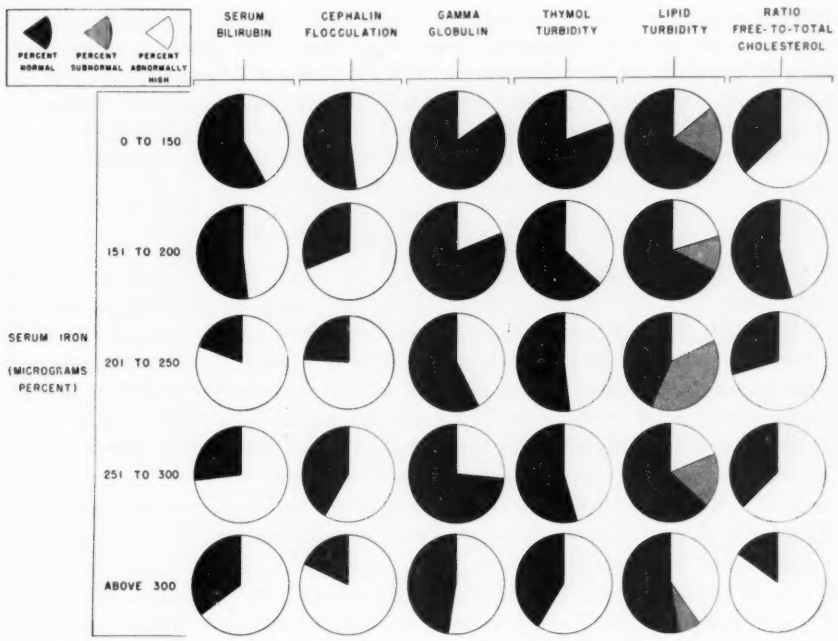

Chart 4.—Relationship between serum iron and selected components of the hepatogram.

results of those tests and the serum iron level. Data presented are based upon the following number of determinations: serum bilirubin, 611; cephalin flocculation, 588; gamma globulin, 642; thymol turbidity, 590; lipid turbidity, 355, and cholesterol partition, 112. The fickleness of function tests in reflecting hepatic disease is again highlighted by this chart—the great majority of the patients studied were proved to have such disease; yet none of the function tests approached being abnormal in a really satisfactory percentage of them. If serum iron values above 200 γ per 100 ml. are arbitrarily accepted as abnormal, then it may be stated that liver disease associated with abnormality in serum iron is likewise associated with abnormality in serum bilirubin, cephalin flocculation, and ratio of free to total cholesterol. Furthermore, serum iron levels above 300 γ per 100 ml. are generally associated with abnormality in all liver-function tests applied in this study.

COMMENT

Serum iron, the transport iron of the body, is nonhematin iron in the ferric state[9] and is bound to beta globulin.[7] There has been advanced no satisfactory explanation of the increase in serum iron that occurs in liver disease, particularly in viral hepatitis. One might speculate that such increases in serum iron are in some way influenced by or dependent upon derangements in either lipid transport or lipid metabolism. This is the circumstantial evidence that encourages such speculation: 1. Beta globulins are concerned in lipid transport.[8] 2. During the clinical course of viral hepatitis and the necrotizing phase of portal cirrhosis a rising lipid turbidity is often coincident with recovery, an event which is, in turn, generally coincident with return of the serum iron to normal levels. It will be recalled in reviewing Chart 1 that these two conditions, at times histologically quite similar, cause the most consistent elevation in serum iron, with the exception of hemochromatosis. 3. In our series of 350 liver biopsies, fatty metamorphosis has been the condition most frequently associated with siderosis of the liver. Perhaps in those observations lies a clue to the cause of serum iron elevation in liver disease that might be further explored by application of newer investigative tools, such as paper electrophoresis, chromatography, and radioiron studies.

CONCLUSIONS

1. Of the liver diseases studied, viral hepatitis causes significant elevation in the serum iron more consistently than does any other disease except hemochromatosis.

2. Although random elevations of serum iron occur later in the disease, maximum elevation occurs during the third week of viral hepatitis. Prior to the third week values tend to fall within normal range or are not sufficiently elevated to be diagnostic. Values tend to return to normal after the eighth week of the disease.

3. In viral hepatitis the serum iron roughly parallels the clinical course; i. e., it is high during the period of greatest morbidity and decreases as the patient improves. However, there is no constant correlation between serum iron and severity of the disease. Nor is there a constant correlation between serum iron and other hepatic function tests.

4. In most diseases of the liver associated with jaundice (unless jaundice is due to hemolysis) it is thought that marked elevation of serum iron is highly indicative of viral hepatitis, especially if values are persistently elevated. The critical serum iron level in this respect is 300 γ per 100 ml.

5. It should be noted, however, that significant elevations of serum iron are not unusual in other diseases of the liver, particularly various hepatitides and the necrotizing phase of portal cirrhosis. On the basis of our data, the increase in serum iron is roughly proportional to the extent of hepatocellular damage.

6. It is thought that determination of serum iron is of particular value in differentiating between viral hepatitis and extrahepatic biliary obstruction, especially during the phase when hepatitis exhibits obstructive phenomena.

7. Determination of serum iron is not proposed as a hepatic function test of such specificity that a single value assumes diagnostic importance. Rather, it is proposed as an adjunct to other function tests and liver biopsy in the investigation of hepatocellular damage. In certain diagnostic situations it may have, however, greater specificity than either other function tests or biopsy.

8. Determination of serum iron is a simple procedure, well adapted to use in the clinical laboratory.

SUMMARY

Results of 659 serum iron determinations in 313 persons in various hepatic states are discussed, and it is established that hepatocellular damage tends to be associated with some degree of elevation in the serum iron level. Excepting hemochromatosis, viral hepatitis is the disease most frequently associated with spectacular increases in serum iron; therefore, the test assumes clinical importance in the differential diagnosis of liver disease associated with jaundice. It is of particular value in differentiating between viral hepatitis and extrahepatic biliary obstruction. Data are presented graphically.

Mrs. Frances B. Abadie, Miss Beryl Kline, and Miss Regina Noel gave technical assistance. Mr. F. W. Busic and Mr. W. D. Bohon did the photographic work.

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CHRONIC BARBITURATE INTOXICATION

Further Studies

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ISBELL and co-workers, in 1950, showed that the behavior and neurological status of five patients experimentally intoxicated with large amounts of barbiturates for 92 to 144 days resembled that of patients chronically intoxicated with alcohol. Also, convulsions and/or a delirium followed abrupt withdrawal of barbiturates from these chronically intoxicated persons. The purpose of the present communication is to extend the series of Isbell and co-workers, from 5 to 19 cases, in order that the variations in the clinical picture of barbiturate addiction, withdrawal, and recovery can be more completely delineated. In addition, a larger series would provide sufficient controls to permit evaluation of therapeutic regimens.

SUBJECTS AND METHODS

Five of the subjects included in this study were those used by Isbell and co-workers,[1] and they have been identified in both reports by the same code numbers, S1, S2, P3, P4, and A5. Fourteen additional male volunteers in general good physical state were selected for study shortly after their admission to the U. S. Public Health Service Hospital, in Lexington, Ky. All gave histories of addiction to opiates and chronic intoxication with large amounts of barbiturates, but, after the study was completed, Patients 7, 11, and 16 retracted the history of barbiturate intoxication prior to admission. None of the patients studied had personal or familial histories of epilepsy or psychoses.

The patients were continuously observed in a special closed ward throughout the study. The precautions taken have been described by Isbell and co-workers.[1]

Since the patients were all addicted to opiates as well as being chronically intoxicated with barbiturates, it was necessary to convert their mixed addictions to a chronic intoxication with a single barbiturate. Following transfer to the special ward, secobarbital was administered orally six times daily in the highest dosage compatible with safe ambulatory management. Secobarbital was chosen as the drug to be used in these investigations because our patients seem to prefer this barbiturate to all others. Methadone was substituted for whatever opiate the patient had been using, and then it was gradually withdrawn over a period of 10 to 14 days; thereafter, no opiates were prescribed. Administration of secobarbital was continued at the same level during and after withdrawal of methadone. The nutritional status of all patients was evaluated. All received supplements of milk and fruit juice in addition to a liberal hospital diet and, when

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indicated, multivitamin capsules (hexavitamin, U. S. P.) were prescribed. None of the patients was considered to have any significant nutritional impairment at the time barbiturates were withdrawn.

Dosage.—The average daily dosages of barbiturates and the length of the intoxication period are shown in Table 1. The Table also gives an estimate of the number of days the patients had been consuming barbiturates prior to admission to the hospital.

RESULTS

Chronic Intoxication.—The signs and symptoms of maintained barbiturate intoxication resembled those of intoxication with alcohol. The symptoms included confusion, difficulty in thinking, impairment of judgment, marked swings in mood

TABLE 1.—*Summary of Dosage During Chronic Barbiturate Intoxication*

Case No.	Drug	Body Weight, Kg.	Average Daily Dosage, Gm.	Days Intoxicated in Hospital	Days Intoxicated Prior to Admission *
S1	Secobarbital	70.3	1.24	91	0
S2	Secobarbital	76.6	1.8	132	0
P3	Pentobarbital sodium	70.3	1.8	119	0
P4	Pentobarbital sodium	72.8	1.3	144	0
A5	Amobarbital sodium	79.0	3.8	104	0
6	Secobarbital	59.9	1.34	48	180
7	Secobarbital	56.8	0.9	46	0
8	Secobarbital	57.0	1.1	43	21
9	Secobarbital	56.4	1.75	35	60
10	Secobarbital	56.6	2.1	48	100
11	Secobarbital	62.7	1.5	41	0
12	Secobarbital	59.9	1.0	38	..†
13	Secobarbital	61.5	1.3	36	60
14	Secobarbital	72.1	2.2	53	100
15	Secobarbital	59.4	1.4	42	270
16	Secobarbital	73.0	1.2	38	0
17	Secobarbital	76.5	1.9	38	210
18	Secobarbital	84.0	1.7	41	45
19	Secobarbital	69.8	1.26	32	30

* Cases S1, S2, P3, P4, and A5 were observed for an extended period without drugs prior to experimental chronic barbiturate intoxication. In cases 6 to 19, inclusive, the figures represent an estimate of the number of days which these patients were continuously chronically intoxicated prior to admission to the hospital. The history and tolerance of the patient for barbiturates were used in arriving at this estimate.

† In case 12 the history was too unreliable to permit an estimate of prior intoxication.

with alternation between elation and depression, increased irritability, and decreased ego control (fighting, weeping, etc.); marked regression in behavior was the rule. The patients neglected their persons and living quarters, and some became infantile and had to be fed by the attendants. The neurological signs included dysarthria, nystagmus, ataxia in gait and station, past-pointing, and diminished or absent skin reflexes. The amount of sleep in 24 hours was not excessive, averaging 7.7 ± 1.37 hours per day during the last 30 days of intoxication. No great changes in weight were observed.

Marked variation in the degree of intoxication and tolerance was observed in different persons. Thus, Patient 14 could consume 2.2 gm. of secobarbital daily and, even with this enormous intake, was able to converse coherently and to walk about without staggering. Patient 12, on the other hand, was extremely drunk and frequently semicomatose on a dosage of only 1.0 gm. daily. In most instances, a

"ceiling" dosage of barbiturate could be established for each person, which could not be exceeded by even 0.1 gm. of barbiturate daily without the degree of intoxication becoming dangerously increased. Frequently, the "ceiling" dosage declined after completion of opiate withdrawal.

Withdrawal.—Withdrawal of barbiturates was abrupt and complete, and no treatment whatever was administered except in Cases S1 and 6. These two patients became so exhausted during the withdrawal delirium that their lives were judged to be in danger, and reintoxication with barbiturates followed by slow withdrawal was carried out.

The clinical signs and symptoms observed in these patients following withdrawal can be classified as "major" (convulsions and dilirium) and "minor." Only 3 of the 19 patients escaped both convulsions and delirium. Taken together, the "major" and "minor" symptoms form a very clear-cut clinical entity. In the first 8 to 12 hours after the last dose of barbiturates, the degree of intoxication gradually declined and the patients appeared to be improving. Between the 8th and the 36th hour the "minor" symptoms appeared and increased in intensity. These included (in rough order of their appearance) anxiety, involuntary twitching of muscles, coarse tremor of hands and fingers on intention, progressive weakness, dizziness, distortions in visual perception (walls seem curved, etc.), nausea, vomiting, insomnia, weight loss, and precipitous drops in blood pressure on standing, or even on sitting. All patients lost weight; the minimum loss was 0.5 kg., and the maximum loss, 7.2 kg. A subject was judged to have insomnia when he slept 2 hours or less out of a 24-hour period. If this criterion is used, only 4 of the 19 patients did not have this symptom. Subject 6 went without sleeping for eight consecutive days. Not all patients, of course, exhibited all these "minor" signs and symptoms, but all the subjects in this series had five or six of those listed above. The "minor" signs usually reached maximum intensity in the second day of abstinence and, thereafter, gradually declined over the course of the following 2 to 15 days.

Convulsions of grand mal type developed in 16 of the 19 patients, an incidence of 79%. The earliest convulsion occurred 24 hours, and the latest, 115 hours after the last dose of barbiturates. All but 2 of the 33 seizures experienced by these patients occurred within 78 hours after secobarbital was withdrawn. The greatest number of convulsions observed was four.

Following the convulsive phase, 12 of the 19 patients (63%) developed a psychosis which resembled alcoholic delirium tremens. The delirium was preceded by insomnia and was characterized by disorientation in time and place but usually not in person and by hallucinations which were predominantly visual. The delirium tended to begin and to be worse at night. It usually terminated spontaneously with sleep which lasted several hours. During the delirium, rectal temperature was usually elevated to about 38.1 C. (100.6 F.). The intensity and duration of the delirium varied widely; some patients were delirious for only one day, others for as long as eight days. Some patients reacted quietly to their hallucinatory experiences, sat quietly, held conversations with imaginary persons, etc. In such patients, very close observation was necessary to establish that a delirium was present. Other patients were agitated, screamed repeatedly, and attempted to escape from imaginary tormentors.

Psychological Studies.—Psychological tests were conducted during addiction, withdrawal, and recovery, to assess quantitatively the coordination, reaction time, and motivation, or "set," of 11 of these 19 patients who were intoxicated with secobarbital. Tests were performed four hours after administration of barbiturates, when the acute effects of intoxication usually had subsided. In comparison with a

TABLE 2.—*Incidence of "Major" Symptoms Which Followed Abrupt Withdrawal of Barbiturates*

Case No.	Convulsions, No.	Delirium		
		Present	Duration (Days)	Severity *
S-1	2	Yes	3 †	4
S-2	0	Yes	4	4
P-3	1	No ‡	..	..
P-4	1	Yes	2	2
A-5	3	No	..	..
6	3	Yes	8 †	4
7	2	No ‡	..	..
8	2	Yes ‡	3	2
9	3	Yes	2	1
10	0	No	..	..
11	0	No	..	..
12	4	Yes	5	3
13	1	Yes	1	2
14	3	Yes	6	4
15	1	Yes	8	3
16	1	Yes	5	3
17	4	Yes	5	2
18	2	No	..	..
19	0	No	..	..

* Severity of delirium is graded 1 to 4 as follows: 1, disorientation in place or time and/or hallucinations (visual or auditory) occurring briefly and at widely separated intervals, with complete insight; 2, disorientation in place and time, with visual and auditory hallucinations occurring every hour or so, with transient loss of insight; 3, disorientation in place and time, with visual and auditory hallucinations constantly present; patient preoccupied with hallucinations; no insight but patient not agitated; 4, disorientation in place, time, and, occasionally, in person; constant vivid, frightening hallucinations; complete loss of insight; great agitation.

† Withdrawal was terminated during the psychotic phase by reintoxication with barbiturates, since the life of the patient was considered in danger.

‡ Hallucinations with insight but no disorientation.

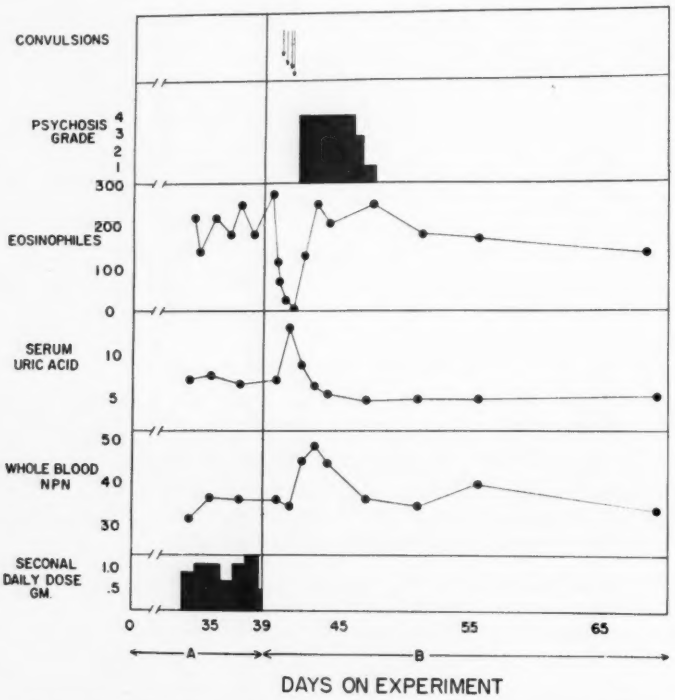
TABLE 3.—*Distribution of EEG Patterns During Barbiturate Addiction, Withdrawal, and Recovery*

Phase of Addiction Cycle	Normal EEG's, %	Abnormal EEG's, %				
		Random	Fast	Mixed Fast and Slow	Slow	Paroxysmal
Chronic intoxication	1.9	9.8	13.8	47.0	27.5	....
Acute abstinence period						
1st to 3rd day	7.2	10.4	....	8.8	33.3	40.3
4th to 8th day	23.3	20.0	....	....	36.7	20.0
Recovery period (9th to 83rd day)	72.7	9.1	....	....	13.7	4.5

control group of persons who were no longer addicts and were not under the influence of drugs, barbiturate addicts had a severe impairment of coordination, as reflected by increased reaction time and a decreased ability to maintain a "set" or readiness to respond. Such persons would be very unsafe operators of automobiles or other potentially dangerous machines. These studies have been reported in detail elsewhere by Hill and Belleville.[2]

Electroencephalographic Studies.—Electroencephalograms, consisting of bipolar and monopolar tracings from frontal, temporal, parietal, and occipital electrodes,

were made on each of the 14 new subjects at weekly intervals during the period of chronic barbiturate intoxication, two to four times on the second day of abstinence and daily thereafter until the electroencephalographic pattern remained stable. An 8-channel Grass electroencephalograph was used. The analysis of 157 records of the last 14 cases is summarized in Table 3. During chronic barbiturate intoxication, 98% of the electroencephalograms were decidedly abnormal. In most subjects mixed rhythmic fast and slow activity predominated, most conspicuously in the frontal and parietal tracings. Other patterns were also observed (Table 3). How-



Relation of (*a*) eosinophile count, (*b*) serum uric acid, and (*c*) nonprotein nitrogen to the clinical course in Case 12 during intoxication with secobarbital (*A*) and during withdrawal and recovery (*B*).

ever, it was not possible to establish a correlation between the specific electroencephalographic pattern and the degree of intoxication observed under clinical conditions.

Very dramatic and abrupt changes in electroencephalograms occurred during the acute abstinence period. In the second day, background activity appeared to change in the direction of increasing "normality" (reappearance of well-sustained alpha rhythms). However, high voltage paroxysmal discharges appeared suddenly in this background in over 40% of the records. Such paroxysmal activity consisted mainly or either high-voltage mixed spikes and slow waves or of well-defined 4 cps spike-and-dome complexes. Almost as often, paroxysmal activity took the form of high-voltage sinusoidal 6 cps discharges, similarly distributed. During the fourth

to eighth day paroxysmal activity decreased, while continuous slow or random delta activity became more prominent in some records; in others, "normal" patterns were observed. By the ninth day of abstinence, when nearly all subjects began to improve markedly from the clinical standpoint, more than 72% were classified as "normal."

Biochemical Studies.—The following biochemical studies were carried out on 15 of the patients: determinations of whole blood and serum nonprotein nitrogen and urea, serum uric acid, creatine, and creatinine. Eosinophile counts were made at appropriate intervals. Determinations were made during intoxication, withdrawal, and subsequent recovery. Typical results on Subject 12 are shown in the Chart. Creatine and creatinine values were not altered during any phase of the addiction cycle; consequently they are not illustrated. The other constituents were not affected by intoxication, since the intoxication values were the same as those observed during the recovery period. The effect of abrupt withdrawal is illustrated in the Chart. Subsequent to four consecutive grand mal convulsions there was a precipitous rise in serum uric acid which was followed by a rise in nonprotein nitrogen. The rise in uric acid was accompanied by a concurrent fall in the eosinophile count from an average of 200 to 0 cells. The eosinophile count returned rapidly to normal even though delirium developed. The changes illustrated by this case were less dramatic in some of the other subjects, but there was usually a transient rise of from 1 to 23 mg. in nonprotein nitrogen level, occurring any time during the third to eighth day of withdrawal. The increase in uric acid and the fall in eosinophile count were related in time to the incidence of grand mal seizures. Maximum changes were observed two to five hours after a convulsion. Unless reinforced by additional seizures, the uric acid level decreased sharply at first, then gradually declined to below control levels. Kidney function, as reflected by phenolsulfonphthalein excretion tests, was normal during withdrawal of barbiturates.

The question arose of whether the elevation of the uric acid level was specific to withdrawal from barbiturates or whether it was directly related to convulsive seizures. To investigate this point, four psychiatric patients who were receiving electroconvulsive therapy were studied. In a series of three electrically induced convulsions at two or three-hour intervals the uric acid values rose about 6 mg. after the second shock. The increase was further reinforced by the third shock of the series. The rise in uric acid was followed by elevation of the nonprotein nitrogen levels. It was concluded that the changes in the uric acid and nonprotein values were not specific to withdrawal of barbiturates but would occur after convulsions from any cause.

COMMENT

Judging from this experimental series of 19 cases, it is obvious that chronic barbiturate intoxication is a dangerous condition and that it resembles chronic alcoholism. Persons taking large amounts of barbiturates are confused and are unable to think clearly, have very poor judgment, and display marked emotional lability. The physician should suspect chronic barbiturate intoxication in a person who behaves like one intoxicated with alcohol but who has no odor of alcohol on the breath.

The present additional series of 14 patients who received secobarbital confirms the previous observations [1] that there is a considerable range among individual per-

sons with respect to the amount of secobarbital required to produce equivalent degrees of intoxication. In this series the range was 0.9 to 2.2 gm. daily.

This series of cases confirms the findings of many authors * that convulsions and delirium will occur following abrupt withdrawal of barbiturates from persons who have been ingesting large amounts of these drugs. The constellation of signs and symptoms observed constitutes a distinct clinical entity, which is best termed the barbiturate-abstinence syndrome. This condition is self-limited, and the patient usually recovers even though no treatment is given. The development of the barbiturate-abstinence syndrome is not dependent on an underlying epileptic diathesis or on any peculiar predilection of morphine addicts to the development of a psychosis. The condition has been observed in many persons who were never addicted to morphine.† Definite abstinence syndromes, including convulsions and very bizarre behavior, have been observed in dogs following withdrawal of sodium barbital after several months of chronic intoxication.[8]

Even though it is well established that dangerous symptoms follow abrupt withdrawal of barbiturates from persons who have been consuming 0.9 gm. (13½ grains) or more of these drugs daily, this fact should be kept in its proper perspective. It does not mean that patients who are taking ordinary therapeutic doses of barbiturates daily under proper medical supervision are addicted. In fact, all available information indicates that no significant degree of the abstinence syndrome occurs after abrupt withdrawal of barbiturates from nonepileptic patients who have been consuming 0.2 gm. of these drugs nightly.[9]

In an attempt to ascertain the minimum daily dose of secobarbital which will produce physical dependence, 0.6 gm. of this drug was administered daily to 18 patients for 35 to 57 days. Two of these patients had one convulsion following abrupt withdrawal of secobarbital, but most of them had only mild or no significant abstinence symptoms.[9]

Very little is known concerning the incidence of symptoms following withdrawal of barbiturates from persons who have been consuming 0.3 to 0.5 gm. of one of the potent barbiturates daily. Studies designed to shed light on this important quantitative aspect of the problem are being undertaken.

The dangerous symptoms of intoxication caused by ingestion of large amounts of barbiturates, the danger of abrupt withdrawal, and the fact that chronic barbiturate intoxication is always associated with a psychiatric disorder mean that the treatment of chronic barbiturate intoxication must be patterned after the treatment of chronic alcoholism or morphine addiction. This implies that such patients should be hospitalized for detoxification and that prolonged psychotherapy is required during and after hospitalization.

At the present time the only method for withdrawal of barbiturates which is known to be safe consists of gradual reduction of the dosage of barbiturates.‡ The importance of proper treatment has been emphasized by the occurrence of deaths during barbiturate withdrawal.§

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* References 3-7.

† References 3-7.

‡ References 10 and 11.

§ References 12 and 13.

SUMMARY AND CONCLUSION

Fourteen men in good general health who were addicted to barbiturates volunteered for an experimental study of chronic barbiturate (secobarbital) intoxication. Barbiturates were administered orally in a dose sufficiently large to maintain continuous moderate to severe intoxication for 32 to 48 days and were then withdrawn abruptly.

The clinical manifestations of chronic barbiturism resemble those of chronic alcoholism.

After abrupt withdrawal of barbiturates, a definite abstinence syndrome developed. The barbiturate-abstinence syndrome is characterized by the disappearance of signs of intoxication, weakness, tremor, great anxiety, anorexia, nausea and vomiting, rapid loss of weight, fever, difficulty in making cardiovascular adjustments on standing, and convulsions of a grand mal type and/or psychosis which resembles alcoholic delirium tremens.

Results of psychological, electroencephalographic, and biochemical studies are reported.

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THROMBOHEMOLYTIC THROMBOCYTOPENIC PURPURA

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THE DISEASE thrombotic thrombocytopenic purpura refers to a condition characterized by an unusual triad: hemolytic anemia, thrombocytopenic purpura, and multiple hyaline thrombi throughout the small vessels of the body. The occurrence of thrombi in cranial blood vessels gives rise to the characteristic cerebral symptoms. Since the name thrombotic thrombocytopenic purpura, first suggested by Singer and co-workers,[11] fails to include any mention of the hemolytic anemia, a modification of this term to thrombohemolytic thrombocytopenic purpura is suggested.

Forty-six cases of thrombohemolytic thrombocytopenic purpura (hereafter referred to as T. T. P.) have been described in the literature up to the present time. As the disease becomes better known, the diagnosis can often be made before death and studies can be carried out on the disease mechanism. An opportunity has been afforded recently to study two cases correctly diagnosed before death. These cases and the associated studies are described below, together with a third case diagnosed at the time of autopsy.

REPORT OF CASES

CASE 1 (NECH 61-808).*—Mr. LaF., a 44-year-old man, was admitted to the New England Medical Center, on Aug. 12, 1951, because of persistent anemia. On admission he was disoriented and confused. Three months prior to admission, tiredness and pallor had begun. One month prior to admission low back pain and a dry, nonproductive cough developed. The patient was discovered to have albuminuria and pyuria. Two weeks before admission he developed extreme pallor, jaundice, confusion, and disorientation. Prior to admission he received six to eight transfusions, with no clinical response.

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Drs. William Dameshek, H. Edward MacMahon, and Mario Stefanini assisted in this study. Dr. Anthony V. Pisciotta provided Figures 3 and 4, and Dr. Zacharias Komninos carried out the search for red cell antibodies.

* This case was previously described by Adelson and Stefanini.[28]

On admission he appeared acutely and chronically ill. He was conscious but confused and disoriented, and he showed some perseveration. The temperature was 99.2 F.; pulse rate, 95; respiration rate, 22, and blood pressure, 115/50. There were bilateral hemorrhages and exudates in the fundi. The sclerae were slightly icteric. There was no adenopathy. Liver and spleen were not felt. A few petechiae were present on the lower extremities.

Laboratory data on admission revealed a red cell count of 1,550,000; hemoglobin, 4.9 gm.; hematocrit level, 18%, and white cell count, 11,700, with a differential count of 75% polymorphonuclear cells, 20% lymphocytes, 3% monocytes, 1% eosinophiles, and 1% basophiles. The red cells showed macrocytosis, spherocytosis, target cells, and "helmet" cells (Fig. 8). The platelet count, by the indirect method,[38] was 23,000. There were 26% reticulocytes. The sedimentation rate was 40 mm. in an hour; a repeated sedimentation rate determination, later in the disease, was 3 mm. in an hour. The plasma hemoglobin was 90 mg. per 100 cc. The osmotic fragility was increased. Tests for red cell autoagglutinins, isoagglutinins, autohemolysins, and isohemolysins, warm and cold, complete and incomplete, were all negative. The mechanical fragility was 23.6%, with a control of 5.1%. Serum bilirubin was 2.8 mg. per 100 cc., with 0.5 mg. direct-reacting and 2.3 mg. indirect-reacting. The fasting blood sugar was 115 mg. per 100 cc. The blood urea nitrogen was 20 mg. per 100 cc. and later rose to 39 mg. Total protein was 6.6 gm. per 100 cc., with 4.4 gm. albumin and 2.2 gm. globulin. Alkaline phosphatase was 1.2 Bodansky units; cephalin flocculation was 4+; thymol turbidity was 3.7 units; the sulfobromophthalein (BSP) test showed 17% retention, and prothrombin time was 14 seconds (50%). The bone marrow was hypercellular, with extreme erythroid hyperplasia (62%). The megakaryocytes were very much increased, but only 6% showed platelet formation (Fig. 3). Many of the megakaryocytes appeared young and somewhat agranular. There were also many megakaryocytes with vacuoles in the cytoplasm (Fig. 4). Iron stains of the marrow showed increased hemosiderin. Tests of hemostatic function revealed a positive tourniquet test, prolonged bleeding time (more than 20 minutes), and poor prothrombin consumption. The urine showed a slight trace of albumin and an occasional fine granular cast. The urine urobilinogen was only 1:20. Hemosiderin was present in the urinary sediment. Subsequent urine samples were rich in red blood cells. A lumbar puncture revealed clear fluid with normal pressure and no increase in cells. However, the spinal fluid protein was elevated to 108 mg. per 100 cc. The colloidal gold test was negative. The EKG showed low T waves in Lead I and inverted T waves in Lead aV_L.

During his hospitalization, the patient developed transient right-sided weakness, with a right Babinski reflex and flattening of the right side of the face. The combination of neurological changes, hemolytic anemia, and thrombocytopenic purpura suggested the diagnosis of T. T. P. A skin and muscle biopsy was performed, but no intravascular platelet thrombi were seen. The patient was started on corticotropin (ACTH), 100 mg. of the Wilson preparation (approximately 200 I. U.) intramuscularly daily for eight days. He showed no response. He received four transfusions of whole blood, but his cell counts did not improve. The reticulocyte count rose to 57.8%, and 19 nucleated red cells per 100 WBC appeared in the peripheral smear. The course was febrile, with temperature up to 102 F. The fever did not respond to penicillin. Heparin sodium (75 mg. every four hours intravenously) was given in the hope of decreasing platelet clumping, but the patient showed no improvement. His confusion became progressively worse; he developed diffuse neurological signs, and on the 11th hospital day he died.

Postmortem Examination (A51-55, NEMC).—Gross Examination: The body was that of a thin well-developed icteric middle-aged white man. There were numerous purpuric areas ranging in size from 0.1 to 1.0 cm. over the thighs, calves, arms, and back. There was no superficial adenopathy. There were no petechiae visible on the serosal surfaces. The heart weighed 350 gm. and was slightly dilated. The epicardium, myocardium, and endocardium were studded with multiple tiny hemorrhages. The valves and chordae tendineae were normal. The right lung weighed 485 gm., and the left, 415 gm. On section they showed slight edema but no hemorrhages. The spleen weighed 250 gm., and its capsule was intact. Section showed a soft cyanotic surface; no follicles were seen. There were no gallstones. The liver weighed 1,710 gm. and appeared grossly normal. Examination of the gastrointestinal tract revealed multiple submucosal hemorrhages in the ileum and colon. The adrenals were unremarkable. Kidneys, ureter, bladder, and prostate were unremarkable. The costal, sternal, and vertebral bone marrow was dark red.

The lymph nodes were not enlarged. The brain weighed 1,390 gm. and was normal in form and consistency. Scattered over its surface were 15 to 20 punctate areas of hemorrhages ranging from 0.2 to 0.5 cm. in diameter. On sectioning, similar widely scattered foci of petechial bleeding were seen within the cortex, white matter, and basal ganglia. The brain stem, meninges, and pituitary appeared normal. The vessels at the base of the brain were patent.

Microscopic Examination: The single outstanding histologic finding was the presence in practically all organs of severe changes in small vessels. The vessels involved were small arterioles, vesse's, and capillaries; the arteriolar and capillary involvement predominated. The lesions consisted of hyaline, granular (Fig. 1), and bimorphous hyaline and granular (Fig. 2) thrombi projecting in a polypoid fashion into the lumina, with varying degrees of occlusion and dilatation of the involved vessels. These thrombi appeared to be firmly attached to the subendothelial ground substance. Some thrombi were covered by a layer of intact endothelium, while others appeared to have a bare surface. In some instances there appeared to have been propagation of the thrombus (Fig. 2). Some thrombi showed varying degrees of organization progressing to recanalization. A few vessels showed only subendothelial deposition of a hyaline

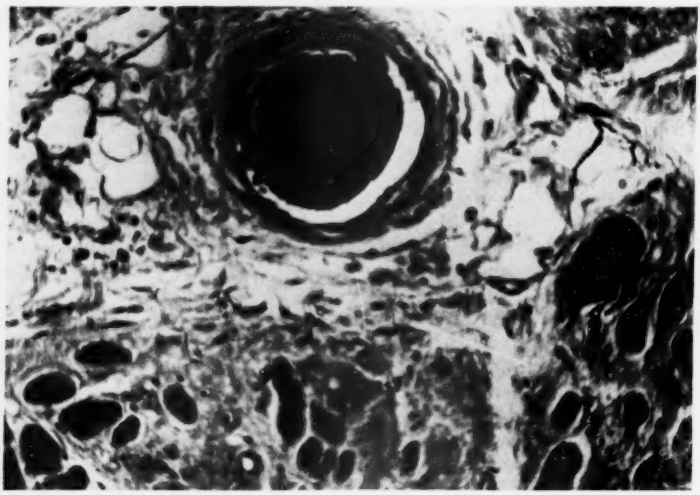

Fig. 1 (Case 1).—Section of heart, including an affected vessel. Note polypoid character of lesion and surface covering of endothelial cells. The vessel is markedly dilated; × 207.

material, with no change in the overlying endothelium. While one might surmise that these intramural lesions antedated the thrombotic phenomena, the histologic evidence was inconclusive. Differential staining on both tissue fixed with formalin and tissue fixed with Zenker's solution, including hematoxylin and eosin, phosphotungstic acid hematoxylin (PTAH), Masson's, Van Gieson's, Weigert's fibrin with periodic acid, Mallory's connective tissue, and iron stains, gave no clue as to the nature of the thrombi. They contained no fibrin, white cells, red cells, collagen, or reticulum. Despite extensive capillary occlusion, especially in the myocardium, cerebral cortex, and adrenal cortex, infarction and hemorrhage were inconspicuous features. There was no leucocytic response to the lesions. Multiple sections of skin, skeletal muscle, lung, and gonads did not show any vascular changes. All other organs showed varying degrees of involvement. The presence of severe antemortem hemolysis was evidenced by hemosiderosis of the spleen and kidney together with marked compensatory erythropoiesis in the bone marrow and spleen. There was a terminal bronchopneumonia. There was moderate cerebral edema.

Case 2 (NECH 69-676).—R. G., a 14-year-old boy, was admitted on June 26, 1952, because of pallor and jaundice. Three months prior to admission he noted the onset of fatigability,

dyspnea on exertion, and spontaneous purpura. Two months prior to admission he noticed jaundice and pallor. Three weeks prior to admission he developed an upper respiratory infection with transient fever, the temperature rising to 100.2 F. The fever subsided after a few days, but the pallor and jaundice persisted. The family history was negative except for the father, who had unexplained hyperbilirubinemia. In this parent, all other liver-function tests and hematologic studies were normal.

Physical examination revealed a well-developed well-nourished alert youth appearing older than the stated age. There was moderate pallor and icterus. There was no adenopathy. The liver was not felt. The spleen edge was felt 2 cm. below the left costal margin. There were a few purpuric spots on the extremities.

Laboratory data on admission included a red blood cell count of 2,380,000; hemoglobin, 7.6 gm.; hematocrit level, 23%; 36% reticulocytes; 66,000 platelets; and 9,500 WBC, with 45% polymorphonuclear cells, 46% lymphocytes, 5% monocytes, 2% eosinophiles, and 2% basophiles. The red cells showed marked variation in size and shape, with many "helmet" cells. Only a very

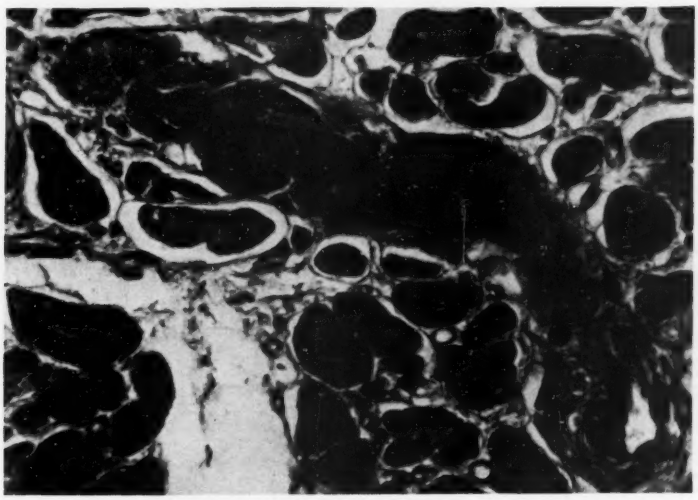

Fig. 2 (Case 1).—Section of heart showing a longitudinal section of an unusually long thrombus. On the left the thrombus has a granular appearance, centrally it is hyaline in type, and to the right it shows endothelial cells organizing the thrombus; × 820.

rare spherocyte was seen. The sedimentation rate was 5 mm. in an hour. The urine was normal on admission; subsequent urine samples showed a trace of albumin, many red blood cells, and occasional granular casts. The urine urobilinogen was 1 : 20.

The bone marrow showed marked normoblastic hyperplasia and increased megakaryocytes, most of which had some granules but no platelet formation (Fig. 3). Autoagglutinins, isoagglutinins, autohemolysins, and isohemolysins, complete and incomplete, warm and cold, were not demonstrable. Coombs' test was negative. Osmotic fragility was normal. Mechanical fragility was 7%, with a normal control of 3%. Urine hemosiderin was 1 + (normal). Plasma hemoglobin was 4 mg. per 100 cc. (within normal limits). Tests for fetal hemoglobin showed less than 1% (normal). Fecal urobilinogen was 620 mg. per day over a three-day period. Total plasma bilirubin was 5.8 mg. per 100 cc., with 0.8 mg. direct-reacting and 5.0 indirect-reacting. Cephalin flocculation was 4 +; thymol turbidity was 1.1 units, and serum iron was 135 γ per 100 cc. An L. E. preparation was negative on two occasions.

The combination of hemolytic anemia with no demonstrable antibody and thrombocytopenic purpura suggested the diagnosis of T. T. P. even in the absence of neurological signs. Accordingly, a muscle biopsy was done; it was reported as showing no platelet thrombi. The patient

was given corticotropin, 100 units per day intramuscularly. Later this was supplemented with simultaneous administration of cortisone by mouth, 100 mg. per day. There was no response to this therapy. On the sixth day of corticotropin therapy the patient developed signs of a massive right cerebral hemorrhage—coma, nuchal rigidity, flaccid left-sided paralysis with apparent loss

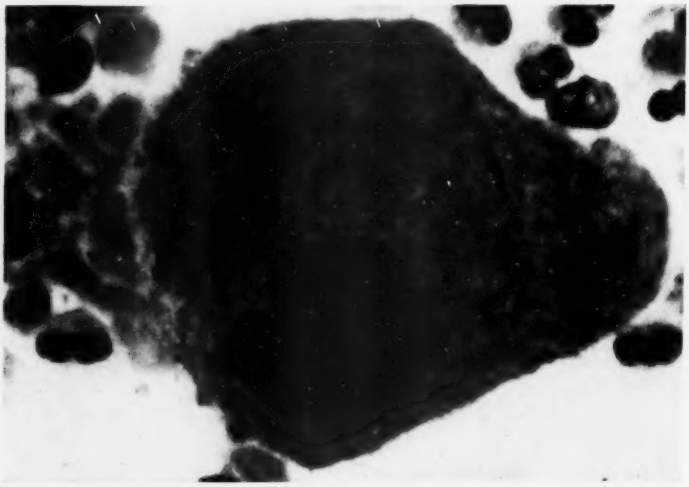

Fig. 3 (Case 1).—Megakaryocyte showing no platelet formation. Similar changes were present in Case 2.

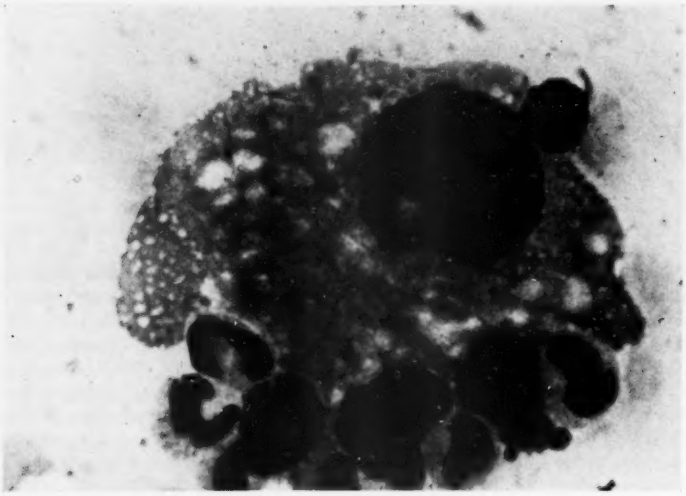

Fig. 4 (Case 1).—Megakaryocyte showing vacuoles in the cytoplasm.

of sensation on the left, and a positive Babinski reflex, also on the left. Lumbar puncture revealed a pressure of 140 mm.; total protein, 65 mg. per 100 cc.; chlorides, 119 mEq., and sugar, 97 mg. per 100 cc. Only two lymphocytes and no red cells per cubic millimeter were seen. For the first time, the patient developed a fever (temperature to 105 F.). On the fifth day after their

onset the neurological signs began to subside, and eventually they disappeared entirely. During this time the patient received repeated platelet transfusions, with no appreciable clinical effect. On July 19, 1952, a splenectomy was performed. Postoperatively, there was no response either in the red cell or the platelet count. He was given plastic-bag blood daily for a total of 25 units during his hospital stay; at no time did his red cell count go above 3,000,000. He also received transfusions of platelet-rich plasma without response. Signs of fluid in his abdomen developed, and it was thought that postoperative intraperitoneal and perhaps left pleural bleeding was developing. In spite of antibiotics, the patient once again became febrile. Terminally the patient had up to four normoblasts per 100 WBC. He also showed leucocytosis (53,000 WBC, with 69% polymorphonuclear cells, 8% lymphocytes, 2% monocytes, 13% metamyelocytes, and 8% myelocytes). He died on the 10th postoperative day.

Postmortem Examination (A52-52 NECH).†—Gross Examination: The body was that of a well-developed young adolescent boy. There were generalized pallor of skin and mucous membranes and marked icterus of skin and sclerae. Petechiae and ecchymoses were present over the neck, arms, thorax, groin, lower extremities, and gluteal areas. There was a left abdominal splenectomy incision, with sutures still in place. There were no palpable superficial lymph nodes.

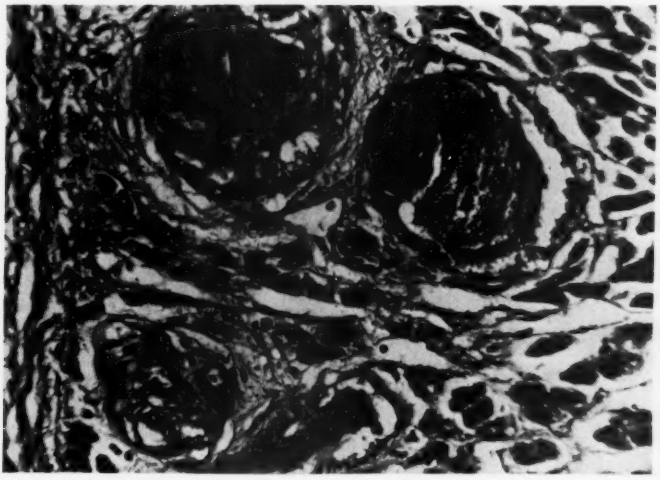

Fig. 5 (Case 2).—Adrenal cortex. There is considerable variability in the character of the lesions. The one in the lower left is almost completely organized by endothelial cells. Other lesions show varying degrees of organization, the one in the right midfield being perhaps the most recent, having a bimorphous hyaline and granular appearance with only occasional endothelial cells; × 415.

There was 3,000 cc. of bloody fluid in the peritoneal cavity. The liver was at the costal margin. The spleen had been surgically removed. A large blood clot occupied the splenic area and the adjacent retroperitoneal tissues. There were ecchymoses on the surface of the small intestine. The left pleural cavity contained 300 cc. of bloody fluid. There were many pericardial petechiae. The heart (370 gm.) was normally formed but slightly dilated, with no valvular abnormalities and no vegetations. There were petechiae in the myocardium and endocardium. The lungs (right, 580 gm.; left, 415 gm.) showed slight edema and dependent congestion. There were a few pleural petechiae over the lower lobes. The liver weighed 2,450 gm. and was tannish-brown and homogeneous. The small and large intestine showed numerous mucosal petechiae and ecchymosis, with considerable blood in the lumen. The adrenals appeared normal. The kidneys (right, 190 gm.; left, 210 gm.) were healthy except for bleeding into the left renal pelvis. Ureters, bladder, prostate, urethra, and testes were unremarkable. The costal, vertebral, and sternal

† The autopsy was performed by Drs. Mandelstam and Lataroca.

marrow was red-brown. The thyroid appeared normal. There was slight generalized lymphadenopathy. The brain weighed 1,490 gm. Its surface was normal, but sections showed multiple petechiae through the hemispheres, brain stem, and spinal cord. The pineal gland and pituitary were not remarkable. The meninges appeared healthy. The vessels at the base of the brain were grossly normal. The spleen (S-52-1855) weighed 260 gm., was normally formed, and presented a purple soft cut surface.

Microscopic Examination: There were minute lesions in arterioles, capillaries, and venules. As in the previous case, several types of lesions were seen (Figs. 5 and 6). These included (*a*) vessels showing only a hyaline alteration of the subendothelial ground substance, (*b*) vessels showing subendothelial hyaline masses elevating the endothelium and bulging into and distending the lumen, and (*c*) vessels showing larger hyaline, granular, and bimorphous hyaline and granular polypoid masses, some of which were endothelized and others of which were devoid of endothelium. Differential stains on tissue fixed with Zenker's solution and with formalin (see Case 1) gave no clue as to the composition or pathogenesis of the lesions. Some organs showed an extraordinary degree of vascular occlusion; yet infarction and hemorrhage were minimal. Leucocytic response was present only where infarction had occurred. The organs most strikingly

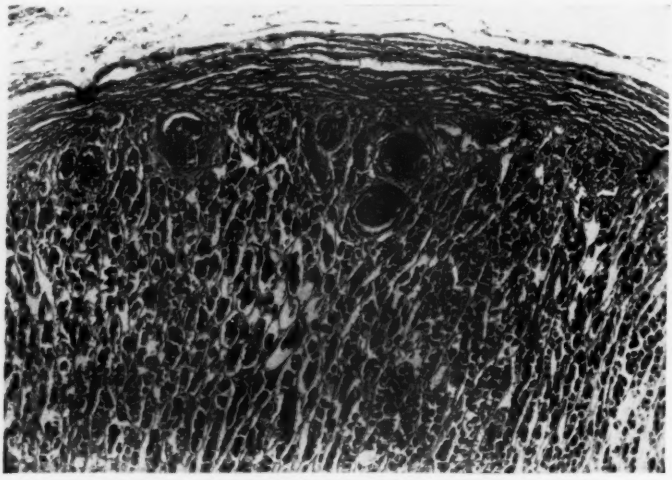

Fig. 6 (Case 2).—Adrenal cortex. Note cluster of lesions under capsule in zona glomerulosa. This low-power view gives a good impression of the marked capillary dilatation associated with the lesions; × 110.

involved were the heart, pancreas, adrenal cortex, and pituitary. No lesions were observed in skin, skeletal muscle, prostate, and lung. The spleen showed the characteristic lesions. Spleen, liver, lymph nodes, and bone marrow showed striking erythropoiesis. There was slight hemosiderosis and considerable erythrocytophagocytosis in the spleen, liver, lymph nodes, and bone marrow. The cerebral cortex showed marked edema, with numerous typical vascular lesions.

Case 3 (TCMS A45-5).—Mrs. C. L., a 36-year-old woman, was followed at another hospital and came to our attention at the time of autopsy. One week prior to admission the patient developed an upper respiratory infection and an associated severe nonproductive cough. Five days prior to admission she noted numbness in her right arm and thickness of speech. On the evening of admission the patient fainted and was found moaning and groaning, unable to speak. She recovered quickly and was promptly hospitalized.

Physical examination on admission showed slight icterus and definite pallor. The liver was felt 2 fingerbreadths below the right costal margin; the splenic tip was just palpable, and there were several purpuric spots over both lower extremities and the left wrist. The remainder of the physical examination and the neurological examination were negative.

Laboratory studies revealed a red cell count of 1,720,000; 35.9% hemoglobin, and 14,300 WBC, with a differential count of 57% polymorphonuclear cells and 43% lymphocytes. Of the 57% polymorphonuclear cells, 12% were band cells. The peripheral smear showed much polychromatophilia. No platelets were seen. The urine showed 3 + albumin, a few coarse granular casts, and 6 to 8 RBC per high-power field. A lumbar puncture revealed slightly increased pressure. Cerebrospinal fluid cell count and protein were normal.

The patient went progressively downhill; she did not respond to transfusions, became comatose, and died on the fifth hospital day, with the clinical diagnosis of "fulminating sepsis."

Postmortem Examination (TCMS A45-5).‡—Gross Examination: The body was that of a well-nourished slightly icteric middle-aged white woman. External examination revealed slight ankle edema. There were no cutaneous petechiae. The peritoneal cavity contained 25 cc. of unclotted bloody fluid. There was slight enlargement of spleen and liver. Each pleural space contained 25 cc. of watery blood-tinged fluid. The heart (275 gm.) was normally formed but very flabby. Many tiny fresh hemorrhages were scattered throughout the edematous epicardium and myocardium; the endocardium, valves, chordae tendineae, and coronary vessels were grossly normal. On section the lungs (right, 900 gm.; left, 800 gm.) showed edema but no localized lesions. The spleen (300 gm.) had an intact capsule and a soft purple pulp. The liver (1,700 gm.) was grossly normal. Aside from tiny hemorrhages into the fundus of the stomach, the gastrointestinal tract was normal. The adrenal glands were not remarkable. The kidneys (right, 150 gm.; left, 150 gm.) were normal except for a few pin-point hemorrhages into each pelvis. The costal, sternal, and vertebral marrow was red and plentiful. The lymph nodes were grossly healthy. The brain was diffusely edematous (1,400 gm.), and the gyri and sulci were flattened. There was one small pia-arachnoid hemorrhage on the surface of each cerebral hemisphere. No localizing lesions were observed in the cerebral hemispheres, brain stem, or pituitary gland. The vessels at the base of the brain were unremarkable.

Microscopic Examination: The microscopic studies revealed lesions similar to those in Cases 1 and 2. Despite widespread partial and complete occlusion of small blood vessels throughout the body, there was only slight and inconstant infarction and hemorrhage. Changes in venules, capillaries, and arterioles included hyaline alteration of the subendothelial ground substance and polypoid hyaline, granular, and bimorphous thrombi showing varying degrees of endothelization and aneurysm formation. No lesions were observed in lung, skin, uterus, gonads, or skeletal muscle. Cardiac involvement predominated. Histologic evidences of hemolysis were present in the form of hemosiderosis of spleen, lymph nodes, and bone marrow; striking erythrocytophagocytosis, and marked erythropoiesis in bone marrow, spleen, and liver. The marrow was markedly hypercellular, and megakaryocytes were abundant. Marked cerebral edema was present. There was a severe terminal bronchopneumonia. Differential staining of tissue fixed with Zenker's solution and with formalin gave no positive information concerning the composition of the occlusive masses.

REVIEW OF THE LITERATURE

Including the three cases which we are reporting, there has been a total of 49 cases of T. T. P. described in the literature. The ages of the patients ranged from 9½ to 69 years; two-thirds of the cases occurred between the ages of 10 and 40. Approximately three out of every five cases have been in females, and, in fact, the first nine reported cases all were in females. Seven of the 49 cases have been in Negroes, the rest in white persons. Table 1 lists chief complaints in order of frequency.

The past history of these 49 patients reveals 9 cases with a previous history of rheumatic fever § or rheumatoid arthritis,|| 3 with previous renal disease,¶ 2 with

‡ The autopsy was performed by Dr. MacMahon.

§ References 4, 12, and 26.

|| References 4, 8, and 23-25.

¶ References 8, 20, and 25.

thrombophlebitis,# and 2 with positive serologic tests for syphilis.* Many had histories of allergic tendency, including sulfa sensitivity with urticaria,[12] angioneurotic edema,[23] hypertrophic rhinitis,[23] and two cases of penicillin sensitivity.[25] In one case there was strong evidence of iodine allergy or toxicity in the etiology of the disease.[16] Other interesting features in the past histories include one case each of leg ulcers,[25] discoid lupus,[22] pleuritis,[23] Raynaud's phenomenon,[25] recurrent eclampsia,[26] and tuberculosis.[20] One patient had previously been treated with antireticular cytotoxic serum.[23]

Of the 49 patients, 12 had prodromata. Among these are included 10 cases of upper respiratory infections shortly preceding the onset of symptoms, 2 cases of urticaria,† and one of dermatitis.[6] One patient had a smallpox vaccination,[15] and another had an injection of tetanus antitoxin [26] just preceding the onset of symptoms.

The total duration of the disease varied from 54 hours to 10 years. Of the 49 patients, 3 died within 1 week, 10 in from 1 to 2 weeks, 13 in from 2 to 4 weeks,

TABLE 1.—*Chief Complaints*

	Cases	
	No.	%
Neurological	23	47
Malaise, fatigue, weakness, listlessness	16	33
Petechiae, purpura, or other bleeding	12	24
Fever	9	18
Pallor	8	16
Abdominal pain	5	10
Headaches	5	10
Joint pain	3	6
Jaundice	3	6
Nausea and vomiting	3	6
Cough	2	4
Muscle pain	2	4
Leg ulcer	1	2

13 in from 1 to 3 months, 3 in from 3 to 6 months, 2 in from 6 to 12 months, and 5 in from 1 to 10 years. Some of these last five are subject to doubt as to diagnosis [8] and as to the actual extent of the T. T. P. phase of the illness,[23] but in one [22] the diagnosis of T. T. P. was based on the pathological appearance of the spleen, removed two and one-half years prior to death.

In only two of the 49 cases ‡ was fever absent. In the other cases the maximum temperature ranged from 102 to 107 F. Of the 49 cases, 44 had neurological manifestations, while in 5 none were present. The neurological symptoms and signs were characteristically multiple, diffuse, and transient; they included disturbances in state of consciousness, motor paralysis, seizures, and, rarely, evidence of spinal cord or peripheral nerve damage.[40]

Of the 49 patients 8 had splenectomies. In one [22] there was improvement after the operation. In the others the disease was basically unchanged. Eight patients have been treated with corticotropin (ACTH) or cortisone, and in none did signif-

References 23 and 25.
* References 8 and 23.
† References 2 and 12.
‡ References 12 and 42.

icant improvement occur. In one of our cases, heparin, as had been previously suggested by Singer and co-workers [11] and Hauser and associates,[21] was tried; no improvement resulted.

The intravascular lesions have been sought in various biopsies. Four muscle biopsies have been done,§ including two by the present authors; all have been negative. Cooper and associates [27] reported two cases diagnosed before death by vessel lesions found in aspirated bone marrow. However, one bone marrow biopsy was reported to be negative [18] and one marrow aspiration contained no arterioles.[41] In addition, one skin biopsy was positive [28] and one liver biopsy was negative.[23] A loop of bowel was removed from one patient because of infarction, and this material revealed the characteristic lesions.[8]

When splenectomy has been done, the surgical specimen has occasionally been reported as normal. Later, after autopsy results were learned, restudy of the spleen

TABLE 2.—*Symptoms*

	Cases	
	No.	%
Malaise, weakness, tiredness, fatigue	24	49
Urinary symptoms, including hematuria	20	41
Headache	19	39
Nausea and vomiting	13	27
Jaundice	12	24
Pallor	12	24
Abdominal pain	11	22
Fever	10	20
Joint pains	8	16
Anorexia	8	16
Cough	7	14
Back pain	7	14
Weight loss	3	6
Congestive failure	3	6
Butterfly rash like L. E.	2	4
Puffiness of face	2	4
Chest pain	2	4
Macular rash	2	4
Major gangrene	2	4
Hives	1	2

sections has revealed the lesions. For this reason, several authors || have studied the spleens in cases presumed to be idiopathic thrombocytopenic purpura, but they have been unable to discover any additional cases of T. T. P. The diagnosis of T. T. P. has been made correctly 14 times before death—7 times by clinical picture, 5 times by splenic histology, and twice by aspirated marrow embedded in paraffin and sectioned.

The various symptoms in the 49 reported cases, exclusive of neurologic and hemorrhagic features, are listed in Table 2. Many of the cases have presented unusual pictures. Case 2 of Gitlow and Goldmark [4] showed the clinical picture of combined rheumatic fever, syphilis, and renal disease. Case 2 of Fitzgerald and co-workers [12] presented as rheumatic fever with urticaria. Two patients had simulated psychoses—that of Epstein and co-workers [13] (schizophrenia) and that of Goldenberg and co-workers [19] (depression). Beigelman's [23] Case 1 presented as

§ References 23 and 24.

|| References 2, 7, and 12.

a collagen disease. Case 1 of Gendel and co-workers [25] presented as lupus erythematosus. Gendel's Case 2 and the case of Blackman, Cohen, and Watson [24] both presented as renal disease. It is of interest that in spite of the multiple thrombi pathologically, gangrene developed in only two cases; in Case 1 of Gendel and co-workers [25] gangrene of a toe developed, and in the case of Brown and Norman [8] a gangrenous volvulus of the bowel developed.

Of the 49 cases, 10 had no history of bleeding tendencies. The hemorrhagic manifestations of the remaining 39 cases are listed in Table 3.

On physical examination, the liver was palpably enlarged in 13 and the spleen was enlarged in 16 of the 49 cases. A few isolated lymph nodes were felt in eight of the cases, but in only two instances (Fitzgerald and co-workers,[12] Case 3, and Barondess,[26] Case 2) was there a significant generalized lymphadenopathy. Skin hemorrhages were mentioned in 34 cases and retinal hemorrhages in 15 cases. Five cases also showed exudates in the fundi, and four showed papilledema. One case showed multiple leg ulcers on admission.[25] Hemic murmurs were common. In addition, one patient had a gallop rhythm,[13] one had a pericardial friction rub,[4] and several had hypertension.

TABLE 3.—*Hemorrhagic Manifestations*

	Cases	
	No.	%
Skin and mucous membrane (petechiae and purpura)	26	53
Gross hematuria	17	35
Melena	12	24
Hematemesis	9	18
Epistaxis	7	14
Vaginal bleeding	6	12
Hemoptysis	3	6
Conjunctival hemorrhages	1	2

The red cell count was given in 40 of the cases. The lowest count was 1,080,000, in Case 2 of Meacham and co-workers [22]; the highest counts were 5,490,000, in the case of Brown and Norman,[8] and 4,020,000, in Case 1 of Green and Rosenthal.[15] In all other cases, the red cell count was below 4,000,000. The hemoglobin ranged from 18% (Baehr and co-workers,[2] Case 1) to 78%.[8] In general, the cases showed a severe normochromic normocytic anemia. The red cells usually showed extreme anisocytosis and poikilocytosis. In 25% of the cases the peripheral smear showed nucleated red cells—up to 55 per 100 WBC. The peripheral smear also showed marked polychromatophilia, and this was mirrored in the reticulocyte counts. In the 29 cases in which reticulocyte counts were available, 28 showed an elevation, up to a maximum of 80% (Gitlow and Goldmark,[4] Case 1). Spherocytes were seen in six cases, and, as Singer has pointed out, they are often intermittent in occurrence in any one case.

The white cell count was given in 39 cases. In 27 cases the count was above 12,000, and in 5 cases, above 30,000. The highest count was 53,000, in our Case 2. Some of the high counts are probably exaggerated by the nucleated red cells, which appear as white cells in the white cell counting chamber. However, in some instances, corrections were made for this (Singer). In three cases, leucopenia developed during the course of the disease. The differential white blood cell

counts were given or described in 41 cases. In 38 cases there was a leukemoid reaction, with a shift to the left, in the white cell series. In 16 cases myelocytes or metamyelocytes were described, and in 5 cases blast cells were seen.

The platelets were described or counted in 43 cases. In one case (Gendel and co-workers,[25] Case 1) they were only slightly reduced—289,000 at one time and 715,000 at another. Two other cases, Case 2 of Gendel and co-workers [25] and Case 2 of Beigelman,[23] showed normal or near normal counts at some time in their course. But at other times these two cases and all the other cases in which platelets were described showed severe thrombocytopenia. In one case [16] they are described as being completely absent. In most other cases the counts ranged from 10,000 to 100,000.

The marrow was described in 22 cases. Of these 22 cases, 14 showed erythroid hyperplasia and 4 showed a shift to the left in the granulocytic series. One showed a decrease in the erythroid series, and two showed erythrophagocytosis. The megakaryocytes in these cases will be discussed below.

The urine was described in 44 cases. Of these, 30 had albuminuria, 35 had red cells in the sediment, and 14 had casts. Urine urobilinogen was tested in 17 cases, and, interestingly enough, in only 8 was there significant elevation. Fecal urobilinogen was tested in four cases and found to be elevated in all four. The most marked elevation was in our Case 2, with 620 mg. per day. Serum bilirubin or the icterus index was reported in 32 cases; in only 4 was the level within normal limits; all others showed increases, up to 17.9 mg. serum bilirubin and 50 icterus index. The erythrocyte sedimentation rate was tested in 14 cases. In six cases the rate was 20 or less; in seven cases, 20 to 40, and in only one case, over 40. A lumbar puncture was performed in 23 cases. Normal results were obtained in 12 cases. In the remaining 11 cases the most common finding was increased spinal fluid protein. A few also showed slight increase in lymphocytes. The blood urea nitrogen or nonprotein nitrogen was determined in 31 cases. In 10 the results were normal; in the remainder they were increased, to a maximum of 180 mg. BUN and 110 mg. NPN.

A great number and variety of laboratory tests were performed in these cases; these will not be enumerated or discussed here. One point, however, is of interest; of the four cases [27] in which a heterophile agglutinin was sought, two cases were found to have a significantly elevated titer—1:112 (our Case 1) and 1:128 (Cooper and co-workers,[27] Case 1). In our case the antibody was characterized as Forssman; in Case 1 of Cooper and his associates the antibody was not further characterized.

PATHOLOGY

The pathognomonic histologic finding in T. T. P. consists of a homogeneous eosinophilic material partially or completely occluding arterioles, capillaries, and, rarely, venules throughout the body. In the original description of the disease, Moschcowitz [1] postulated that these structures were thrombi composed of agglutinated red blood cells. Since then, as more cases have been recognized clinically, attempts have been made to correlate the clinical thrombocytopenia with these thrombi. Baehr and co-workers [2] considered the plugs to be composed of platelets trapped in the small blood vessels, thus producing a fall in the level of circulating platelets. Most subsequent authors have agreed that the plugs are partially or entirely platelets. No specific stains are available for the differentiation

of platelets. Baehr and co-workers [2] and Fitzgerald and co-workers,[12] employing histochemical techniques, concluded, by exclusion, that the intraluminal masses could be platelet thrombi. This work has been repeated by others, including ourselves, with similar findings. Meacham and co-workers [22] and Orbison [39] point out the dangers of concluding that the material is platelets on the basis of differential staining, since the occlusions might represent extruded intramural degenerated material rather than intraluminal coagulum. The problem would be clarified if stains specific for platelets in fixed tissues were available.

In recent years, more and more emphasis has been placed on the associated changes in the walls of the occluded vessels. Altschule [5] first suggested that endothelial cell proliferation might be the primary defect and the platelet thrombosis secondary. This possibility has been supported by subsequent authors.¶ In addition focal degenerative and destructive changes have been recognized in the vessel walls.# Orbison [39] has demonstrated the existence of aneurysmal dilatation or distention of the small arteries and capillaries, a finding also observed by Gendel and co-workers [25] and Cooper and co-workers.[27] These authors consider the vessel wall degeneration, aneurysm formation, and endothelial cell proliferation to be consistent with a primary vascular lesion. The findings in our three cases also reveal a primary change in the subendothelial ground substance of the affected vessels, with or without secondary endothelial proliferation and aneurysm formation (Figs. 1, 2, 5, and 6). It may be that the first step in the process is a change in endothelial permeability, with secondary alterations in the subendothelial ground substance; such a hypothesis has been applied to the vascular lesions of malignant nephrosclerosis, periarteritis nodosa, scleroderma,[43] and, recently, parietal thromboendocarditis.[44] However, definite conclusions cannot be reached, because the staining reaction of the platelets, the intramural lesions, and the intraluminal plugs are similar.[20] Since many of the intraluminal masses have a bimorphous hyaline and granular appearance (Fig. 2), they may represent an extruded intramural material with superimposed platelet thrombi.[20]

While all organs may be involved, the severity and distribution of involvement varies from case to case. A review of the literature, including our three cases, indicates that the organs most extensively affected are the heart, brain, adrenal cortex, lymph nodes, kidney, liver, and spleen. The lungs are rarely involved, and in only one of our cases were thrombi found in the pulmonary vessels. We found no lesions in the skin and skeletal muscle in our three cases. However, Meacham and co-workers [22] found the skin vessels involved in two cases. The skeletal muscle was also affected in one of the cases of Meacham and his associates,[22] in the diaphragm in Gore's five cases,[20] and in both of the cases of Cooper and co-workers.[27] Practically all authors have commented upon the striking lack of infarction, inflammation, and bleeding despite the widespread vascular occlusions. Such has been our experience in these cases. This seeming paradox has been explained by a combination of incomplete occlusion of involved vessels and the lack of complete involvement of the capillary bed * and by the slow process of the occlusion, which allows time for adequate collaterals to be established.[40]

¶ References 7, 9, 10, and 14.

References 9, 10, 20, 25, 27, and 39.

* References 6 and 27.

SPECIAL STUDIES AND COMMENT

I. Thrombocytopenia.—The problem of platelet fate in T. T. P. is still unsolved. Baehr and co-workers,[2] in 1937, first noted the thrombocytopenia and suggested that platelets might be trapped in the periphery, forming the hyaline thrombi seen in the smaller vessels. Baehr carried out histochemical studies to show that the thrombi were consistent with platelets, and these studies have been repeated and enlarged upon by others.† However, it has often been stressed that there is no direct proof that these hyaline thrombi actually do represent platelet material.

The thrombocytopenia has been explained by Baehr and his associates [2] on the basis of increased platelet destruction. Gendel and co-workers,[25] however, have been impressed by the morphologic changes in the megakaryocytes, and they have suggested that decreased platelet production may play a role in the thrombocytopenia. This same problem—increased platelet destruction versus decreased

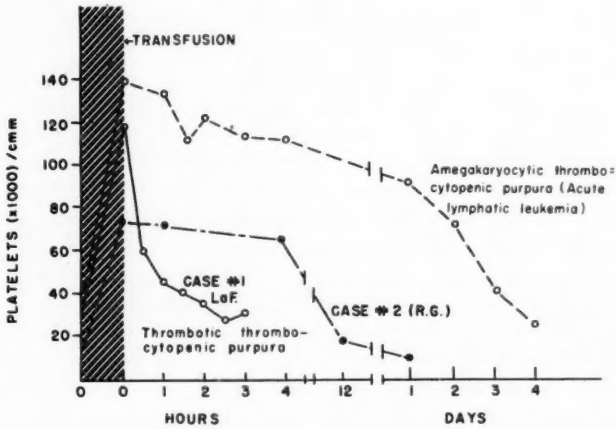

Fig. 7.—Platelet survival studies in Case 1, Case 2, and a patient with secondary thrombocytopenia.

platelet production—has been studied in idiopathic thrombocytopenic purpura (hereafter referred to as I. T. P.) by various methods. We have attempted to apply these same methods to our cases of T. T. P.

In I. T. P., platelet survival has been studied by platelet transfusion techniques.‡ Using the method described by Stefanini and co-workers, we carried out similar studies in T. T. P. We transfused platelet-rich polycythemic plasma into our patients in Case 1 and Case 2 (Fig. 7). Normally platelets will survive three to five days. In Case 1 the survival time was less than 2 hours; in Case 2 it was less than 12 hours. Both cases, then, showed extremely rapid destruction of platelets. Case 1, which showed the shorter platelet survival time, also was the more acute of the two cases; the total duration of illness in Case 1 was three and one-half weeks, as compared with a total duration of four months in Case 2.

† References 7 and 12.

‡ References 32 and 33.

It appears then, that a platelet-destruction mechanism is present in T. T. P. The next problem is whether this mechanism can be demonstrated in the plasma of such patients. In vivo attempts to demonstrate such a mechanism have been successful in I. T. P. Harrington and his associates [36] have shown that when the plasma of some patients with I. T. P. is transfused into normal people the recipients develop a transient thrombocytopenia. This thrombocytopenia occurs in approximately one-half the cases. We attempted to demonstrate this phenomenon in T. T. P. Plasma from Case 2, 250 cc., was transfused into a normal recipient, but no significant thrombocytopenia developed.

We next attempted to demonstrate a platelet-destruction mechanism by in vitro methods. In I. T. P., Stefanini and his associates [31] have shown that some of the cases have demonstrable platelet agglutinins. Using similar methods, we were unable to show a platelet autoagglutinin or isoagglutinin either in Case 1 or in Case 2. Case 1, however, did have an interesting platelet heteroagglutinin.[28] This agglutinin was apparently related to a red cell heteroagglutinin of the Forssman variety. Case 2 did not show this Forssman antibody. In 1943, Bernheim [6] attempted to show a platelet agglutinin in the postmortem serum obtained from her case of T. T. P. She also was unable to show such an agglutinin.

The demonstration of a shortened platelet survival time and, therefore, a platelet-destructive mechanism in T. T. P. fits the original hypothesis of Baehr and co-workers [2] that platelets are trapped in the peripheral vessels, where they form the hyaline thrombi of this disease. However, it should be emphasized that most cases of I. T. P. show a similar platelet-destruction mechanism and yet lack hyaline thrombi.

Of the previous 20 cases in the literature in which bone marrow studies of megakaryocytes were done, 11 are reported as showing normal numbers and 9 are reported as showing increased numbers of megakaryocytes. Six of those 9 are said to show decreased platelet formation, and in one of the cases of Gendel and co-workers [25] there was an increase in young forms of megakaryocytes. Two of the cases with normal numbers of megakaryocytes [27] also showed a shift to the left in megakaryocytes, with a decrease in platelet formation. In our Cases 1 and 2 bone marrow aspirations showed a striking increase in the number of megakaryocytes, together with a decrease in platelet formation (Fig. 3). In addition, in Case 1 there was a partial loss of granules as well as the appearance of vacuoles in the cytoplasm of the megakaryocytes (Fig. 4). We feel that the changes in the megakaryocytes of T. T. P. resemble the changes in I. T. P.[37] As in I. T. P., the cause for these changes is obscure. It may be due to some plasma factor (? antibody) attacking the megakaryocyte as well as the platelet § or it may be due to some humoral factor inhibiting megakaryocytic activity.[37]

II. Anemia.—Trobaugh and co-workers [7] were the first to point out the hemolytic component of T. T. P. More recently, Singer and his associates || have carried out numerous studies on the hemolytic mechanism. In our Cases 1 and 2 we have done similar studies. In Case 1, which was the more severe clinically and in which the platelet survival time was shorter, the hemolytic component also appeared to be more severe. Plasma hemoglobin was 90 mg. per 100 cc., a great many spherocytes were seen (Fig. 8), osmotic fragility was normal, and mechanical fragility was nor-

§ References 31 and 45.

|| References 11 and 18.

mal. In Case 2, the mildest of our three cases, red cell survival was studied by the Ashby method. Singer had previously pointed out that since patients with T. T. P. do not respond to multiple transfusions they must have a shortened survival of transfused red cells. To test this hypothesis, we transfused 1,000 cc. of fresh Type O blood into our patient, whose blood was Type B. By the differential agglutination method, we found that 40% of the transfused red cells were destroyed in one day, and 60% were destroyed by the second day. This demonstrated an extremely active hemolytic process, with an exponential curve as marked as those seen in the severest cases of acquired hemolytic anemia. The severity of the hemolytic component in this case was confirmed by the amount of fecal urobilinogen, 620 mg. per day. This also is as marked as is the fecal urobilinogen value in the severest cases of hemolytic anemia. It is interesting that Singer and his associates,[18] who also carried out fecal urobilinogen studies, found only a slight elevation (118 mg. per day). Gendel and

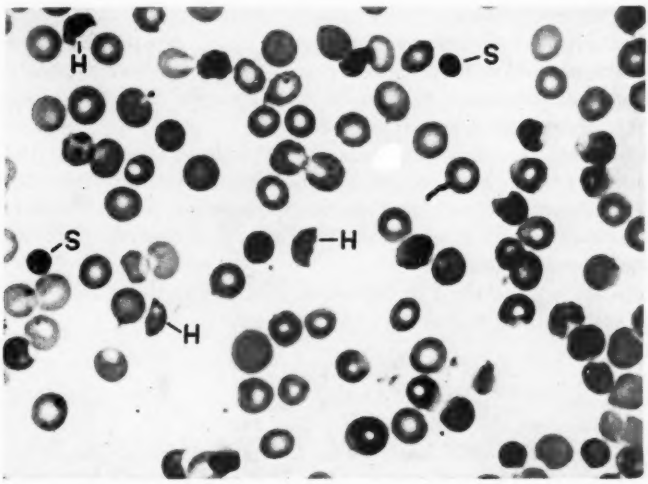

Fig. 8 (Case 1).—Peripheral smear. H, helmet cell. S, spherocyte. Note the anisocytosis, poikilocytosis, and thrombocytopenia.

co-workers,[25] however, found 300 mg. per day, and Meacham and co-workers,[22] found 560 Ehrlich units per 100 gm. (normal control, 192 units).

In spite of the clear evidence of a hemolytic mechanism, all attempts at demonstration of red cell autoantibodies and isoantibodies in Cases 1 and 2 were negative. Neither agglutination nor hemolysis could be shown at 4 C., 22 C., or 37 C.; at acid or normal pH, or in albumin or in saline media. Coombs tests in both cases, using multiple commercial and experimental Coombs sera at full strength and at various dilutions, were also negative. Case 1 did have a Forssman antibody to a titer of 1:112.[28] Case 2 showed a normal titer, however (1:14). One other author [27] has reported two cases in which heterophile agglutinins were sought; in one of these two cases an elevated level (1:128) was found. The explanation for this elevation of heterophile (Forssman) antibody in T. T. P. probably lies in the thrombocytopenia, since it has recently been pointed out that in cases of thrombocytopenia due to various causes such an antibody is often present.[30]

III. Pathogenesis.—We conceive of T. T. P. as an immunohematologic disorder in which an autoimmune process is set in motion against the red cell, platelet, megakaryocyte, and vessel wall. The anti-red-cell process causes hemolytic anemia. The thrombocytopenia is probably due to two factors: (1) increased destruction of platelets, as shown by the shortened survival time of transfused platelets, and (2) decreased production, as suggested by anatomic changes in megakaryocytes. The anti-vessel-wall factor is responsible for the degenerative changes in the wall of the small blood vessels and, perhaps, the intraluminal plugs.

The quadruple threat of T. T. P.—against platelet, megakaryocyte, red cell, and vessel wall—may be due to four separate antibodies. On the other hand, it may be due to a single antibody which cross reacts with the four separate antigens.

SUMMARY

A review of the clinical, laboratory, and pathological data of 46 cases of T. T. P. is presented, together with three new cases.

The mechanism of thrombocytopenia is discussed. No platelet autoagglutinins or isoagglutinins could be found in two cases. Survival time of transfused platelets was shortened in two cases, but plasma from a patient with this disease did not produce thrombocytopenia in a normal recipient.

Although extensive hemolysis was evident, no autohemolysin, isohemolysin, autoagglutinin, or isoagglutinin could be demonstrated. However, Ashby differential agglutination studies showed extremely shortened red cell survival.

A vessel wall lesion, believed to be primary, is described. The nature of the hyaline plugs remains obscure.

The disease is considered to represent a hypersensitivity state involving red blood cell, platelet, megakaryocyte, and vessel wall.

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ALIMENTARY TRACT IN DISSEMINATED SCLERODERMA WITH EMPHASIS ON SMALL BOWEL

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THE PROTEAN nature of disseminated scleroderma has been thoroughly documented.* In the discussion of alimentary tract involvement, the esophagus has been the focus of most attention. The changes in the remainder of the gastrointestinal tract have not been adequately stressed or completely described.

Review of the literature indicates that at least 21 cases with either roentgenologic or pathologic evidence of intestinal involvement by scleroderma have been recorded in sufficient detail to be analyzed.† Although 13 of these cases were subjected to autopsy, there have been few detailed descriptions of the histologic changes in the small intestine and even fewer adequate illustrations. On the whole, the findings were said to consist of replacement by dense collagen of the submucosa and at times of the muscularis, associated with atrophy and degenerative changes, particularly of the smooth muscle. The onset of the disease occurred prior to the age of 40 in about two-thirds of the cases, and the sex distribution was relatively even.

The patients fell into two major symptomatic groups: those with dysphagia and those without dysphagia. In the former group, of 13, dysphagia was usually of long duration. Epigastric fullness, abdominal pain, and nausea and vomiting developed subsequent to the dysphagia, and diarrhea occurred still later in the course of the disease. When present, diarrhea was of grave prognostic import. A sense of bloating and fullness, suggesting dilated intestinal loops, was at times a troublesome and persistent symptom. Pain, when present, was usually epigastric in location, or occasionally diffuse, and was unaccompanied by significant tenderness. In this group, the average duration of the disease from the onset of symptoms was twice as long as in the group without dysphagia.

The second group, of 10 patients, had definite gastrointestinal symptoms but no evidence of dysphagia. Abdominal pain, epigastric fullness, nausea and vomiting, and occasionally diarrhea were present. The duration of symptoms was usually short and the progression of the disease rapid, as compared with that of the first group. In one patient the skin changes developed two years after the onset of the gastrointestinal symptoms.

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* References 1-7.

† References 8-22.

Classic skin findings, such as induration, pigmentation, tightness, shinyness, and smoothness, were present in all cases. Seventeen patients had evidence of the Raynaud phenomenon. Laboratory data were sparse and not distinctive.

Roentgenologically, the esophagus was described as widened, patulous, and somewhat stiffened. Peristalsis was significantly diminished, and narrowing of the distal esophagus, as in esophagitis, was frequently noted. Hiatus hernia was common. The stomach was considered somewhat dilated in a few cases. Varying degrees of dilatation of the small bowel, frequently striking in the second and third portions of the duodenum and the jejunum, were recorded, and delayed motility was common.‡ Sacculation of the large bowel was described in a number of cases,[4] and marked dilatation of the colon was also found in a few instances.

Therapy seemed to be relatively ineffectual in most instances. Thirteen of the 24 patients were dead at the time of report, and 1 was stated to be dying. Five were living, with symptoms, and in an additional five instances it could not be determined whether the patients were living or dead.

Within the past few years we have seen six cases in which widespread involvement of the gastrointestinal tract has been demonstrated radiologically. In the present study the clinical and pathologic data in these cases have been reviewed and correlated with the roentgenologic findings.

REPORT OF CASES

Case 1 (86039).—P. S., a 46-year-old woman, entered the San Francisco Hospital on March 3, 1950, because of pain in the right knee and epigastric distress. For many years she had noted that her hands and feet became blue and painful on exposure to cold. Progressive skin thickening, small digital ulcers, and calcified subcutaneous nodules anterior to both knees developed. The appearance of the skin was typical of scleroderma.

She had had dysphagia for 12 years, with dilatation of the proximal esophagus and narrowing distally, demonstrated roentgenologically as early as 1939. Esophageal biopsy was reported to show esophagitis and "increased density and hyalinization of the submucosal collagen." In June, 1948, resection of her esophagus and gastroenterostomy were performed, with relief of dysphagia. She continued to have moderate epigastric distress, bloating, and bouts of vomiting. Recently, her right knee became reddened and swollen and failed to respond to antibiotic therapy.

Physical Examination.—The patient was thin. The skin of her extremities was shiny, pale, and thickened, with brownish pigmentation in some areas. The face was not involved. Multiple hard subcutaneous nodules were felt over both knees, and the suprapatellar area was tender and inflamed, with multiple fluctuant and pus-filled portions.

Laboratory Data.—Serum calcium was 11.7 mg. per 100 cc.; phosphorus, 3.9 mg. per 100 cc.; alkaline phosphatase, 1.9 King-Armstrong units. Electrocardiogram was normal.

Biopsy of the skin of the right knee, on April 25, 1950, showed calcinosis with chronic ulceration.

Course.—The purulent material anterior to the right knee was drained, and gradual healing of the lesion in the right knee occurred. The patient has been seen a few times subsequently, most recently in February, 1953. Her epigastric distress has increased significantly, although she no longer has difficulty in swallowing. She complains of bloating and occasional constipation.

Roentgenologic Studies (Fig. 1).—There were multiple calcific deposits adjacent to the distal phalanges of the hands. Calcific deposits were also noted anterior to the knee joints bilaterally.

Roentgen examinations of the esophagus and gastrointestinal tract, some of them performed prior to entry, showed the following: 1. 1945, there was some dilatation of the proximal esophagus, with significant narrowing about 2 cm. above the cardia. The stomach and duodenum

‡ References 7 and 15.

were essentially normal. 2. 1948, the esophagus was unchanged. Slight dilatation of the third portion of the duodenum was noted fluoroscopically and on the films. 3. 1953, esophagogastrostomy had been performed, and the site of anastomosis was widely patent. As before, no peristalsis was detected in the proximal esophagus. The stomach was normal. The third portion of the duodenum was significantly dilated, and, at fluoroscopy, stasis was marked. Small intestine motility was normal.

Comment.—This middle-aged Italian woman had skin and esophageal involvement which antedated by many years the involvement of the small intestine. Studies

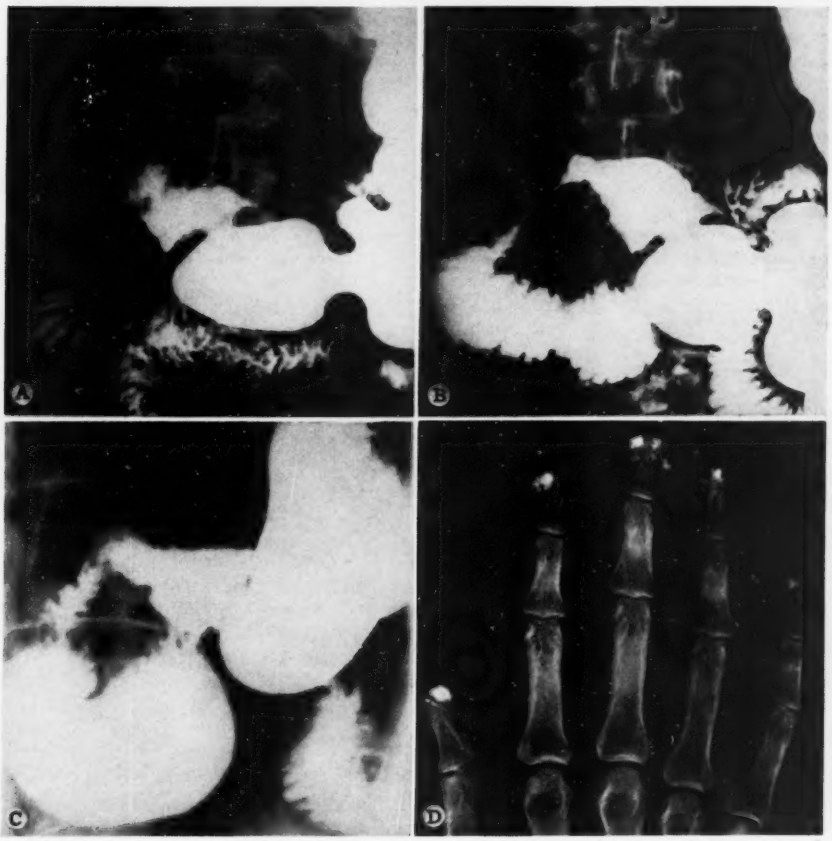


Fig. 1 (Case 1).—Scleroderma. *A*, gastrointestinal series, 1945; the duodenum is essentially normal. *B*, gastrointestinal series, 1948; there is slight dilatation of the third portion of the duodenum, noted fluoroscopically and on the films. *C*, gastrointestinal series, 1953; the third portion of the duodenum shows further dilatation; on fluoroscopy, marked stasis was noted. *D*, typical calcific deposits adjacent to the ungual tufts.

in 1945 showed a normal stomach and duodenum. Three years later there was definite dilatation of the third portion of the duodenum at fluoroscopy and on the films. In 1953 the third portion of the duodenum not only was grossly dilated but had marked stasis and absence of peristalsis at fluoroscopy, the dilatation extending to a point about 6 cm. proximal to the ligament of Treitz. These findings coincided with an increase in symptoms of epigastric pain and bloating.

After partial esophagectomy and esophagogastrostomy her dysphagia was relieved, but her epigastric distress and bloating persisted and became worse. Changes in her small bowel did not develop until at least 10 years after the first evidence of visceral involvement. Although the changes have become more prominent, they remain limited to the duodenum and have not yet involved the remainder of the small bowel.

CASE 2 (295126).—C. L., a 36-year-old woman, entered Stanford University Hospitals on Jan. 3, 1950, because of anorexia and skin changes. About one year previously, she had noted muscular pains and stiffness of her extremities. A few months later, her hands became white on exposure to cold and her skin became taut and indurated, with gradual disappearance of the induration. She also noted marked nausea and anorexia. She developed dysphagia and increasing muscle weakness and noted difficulty in opening her mouth. Increasing weight loss followed.

Physical Examination.—The skin was thin, taut, and atrophic, with bronzing of the extremities. The facial expresion was fixed. There was generalized muscular weakness and some flexion deformity of the elbows. The remainder of the physical examination was noncontributory.

Laboratory Data.—Serum calcium was 10.7 mg. per 100 cc.; phosphorus, 4.4 mg. per 100 cc.; alkaline phosphatase, 1.3 King-Armstrong units. Electrocardiogram was normal.

Biopsy of skin and muscle from the right pectoral area, on Jan. 5, 1950, showed moderately advanced changes in the skin typical of scleroderma. There was diffuse atrophy of the muscle fibers, with focal mononuclear cell infiltration.

Course.—The patient was placed on symptomatic therapy and was discharged. Two months later she was readmitted, started on cortisone therapy, and discharged on a maintenance dose of 75 mg. per day. Her appetite became better, she gained weight, and her physical strength increased. Her fingers became more limber, and definite wrinkles were noted in her skin. After four months of continued cortisone therapy, she developed moderate euphoria and was given corticotropin (ACTH), with maintenance of improvement on 20 to 40 mg. daily. She then complained of increasing stiffness of her fingers, epigastric distress, nausea, and anorexia, and corticotropin was discontinued after nine months. Cortisone was then administered once more, and again her condition improved. She has remained on 25 mg. daily for the last one and one-half years, with no further progress of the disease.

Roentgenologic Studies (Fig. 2).—Examination in 1950 demonstrated difficulty in initiating swallowing, flaccidity and impaired peristalsis in the esophagus, and a normal stomach and small bowel. One year later, in February, 1951, esophageal peristalsis was further impaired and emptying was markedly delayed. The stomach was normal. Peristalsis in the duodenum and proximal small bowel was diminished. There was minimal dilatation of the third portion of the duodenum but not of the remaining small bowel. Marked impairment of motility was present, and at six hours the head of the barium meal remained in the proximal small bowel.

Flexion contractures of the hands were present.

Comment.—In January, 1950, the patient's digestive tract symptoms were referable to the esophagus. Her stomach and small bowel were normal roentgenologically. By February, 1951, five months after the onset of epigastric distress and anorexia, impaired mobility was demonstrable in the small bowel, with diminished peristalsis.

Cortisone produced definite improvement in her symptoms, and she has been maintained on small doses up to the present. One of the striking manifestations of improvement was the increased flexibility of her fingers, shown in her ability to type as well as she had before the onset of her disease.

CASE 3 (96881).—M. K., a 42-year-old woman, entered the San Francisco Hospital on Feb. 13, 1951, because of severe cramping right upper quadrant pain, accompanied by nausea, vomiting, and diarrhea, of one and one-half years' duration. Shortly after the onset of symptoms, she developed constant epigastric distress and distention, associated with flatulence, anorexia, and weight loss. She had had a recent exacerbation of symptoms, with 10 to 12 bowel movements

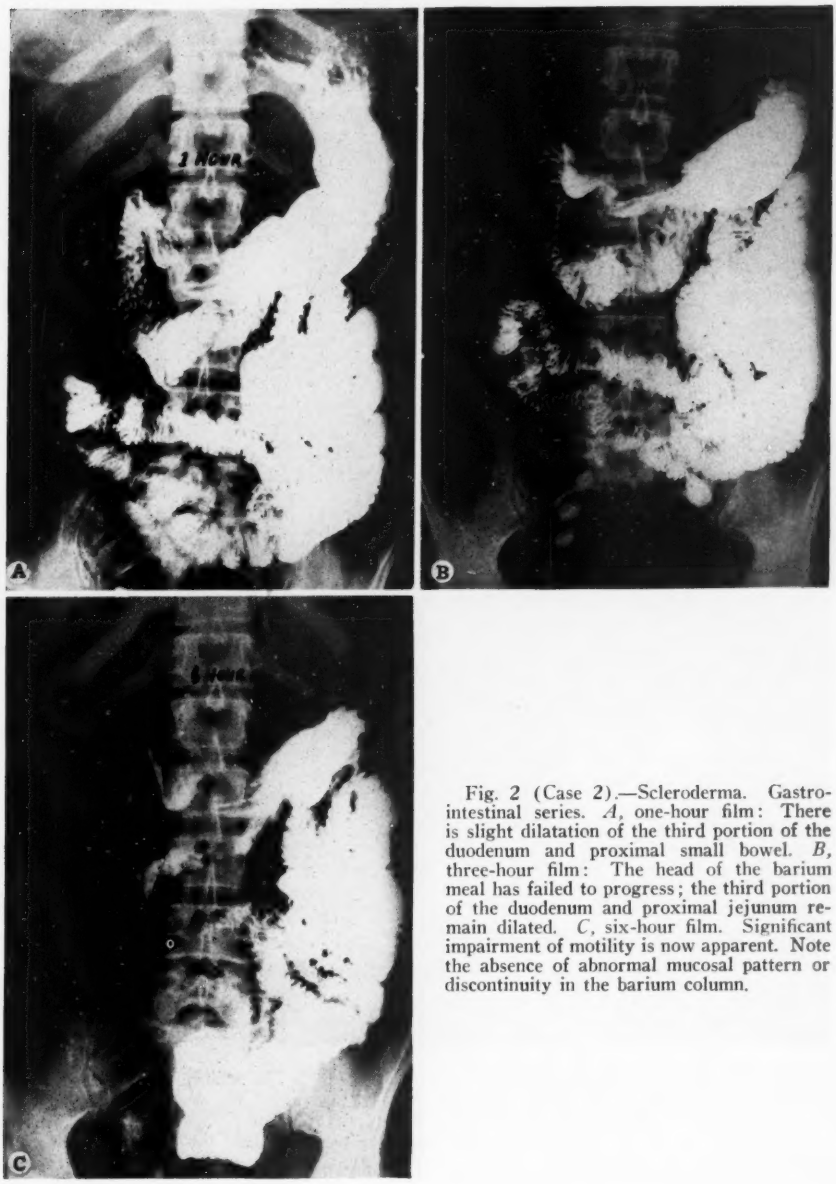


Fig. 2 (Case 2).—Scleroderma. Gastrointestinal series. *A*, one-hour film: There is slight dilatation of the third portion of the duodenum and proximal small bowel. *B*, three-hour film: The head of the barium meal has failed to progress; the third portion of the duodenum and proximal jejunum remain dilated. *C*, six-hour film. Significant impairment of motility is now apparent. Note the absence of abnormal mucosal pattern or discontinuity in the barium column.

daily. She also had occasional leg edema, dyspnea on exertion, and mild orthopnea. She had no difficulty in swallowing. For the past two years, she had noted that her hands and feet blanched on exposure to cold.

Physical Examination.—The patient was thin and chronically ill. Her skin was dry, with poor turgor and brown pigmentation of the arms and thorax. The lungs were clear. A

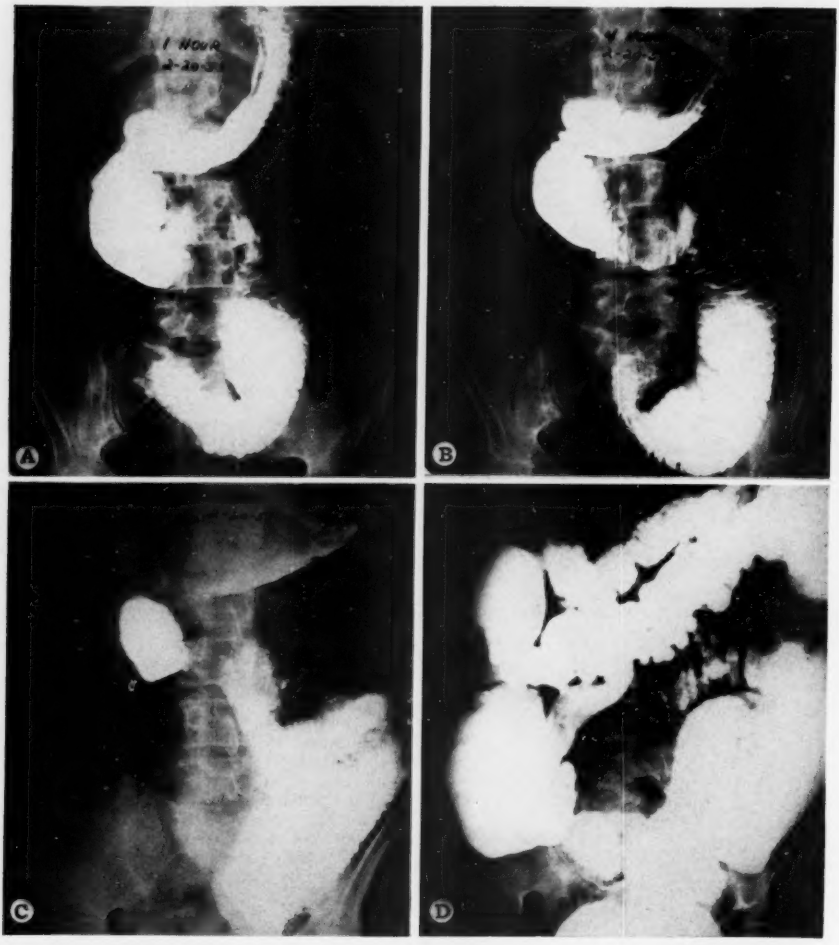


Fig. 3 (Case 3).—Scleroderma. Gastrointestinal series. *A*, one-hour film: There is marked distention of the third portion of the duodenum, as well as of the proximal jejunal loops. *B*, four-hour film. The head of the barium meal has failed to progress; the valvulae conniventes are prominent. *C*, six-hour film. The duodenum remains dilated, and the barium has failed to progress beyond the jejunal loops. There is marked delay in barium passage. *D*, barium enema: There is sacculation of the transverse colon, similar to that described in other cases of scleroderma; the terminal ileum is dilated.

moderately loud systolic murmur was heard over the second and third left intercostal spaces. The abdomen was markedly distended, with no palpable masses or organs.

Laboratory Data.—Hemoglobin was 11 gm.; white blood cell count, 9,600, with normal differential count; blood chemistry studies were essentially normal, except for the glucose-tolerance curve, which was relatively flat. Fasting blood sugar was 62 mg. per 100 cc.; at 45 minutes, 71 mg.; at 2 hours, 70 mg., and at 4 hours, 80 mg. per 100 cc. Her stool was soft, was occasionally guaiac-positive, and showed food residues varying from moderate to marked. Electrocardiogram showed low voltage and abnormal T-waves.

Biopsy of skin and muscle from the left hand on March 3, 1951, showed no definite skin changes typical of scleroderma, but there was mild sclerosis of the subcutaneous adipose tissue and diffuse atrophy of the muscle fibers.

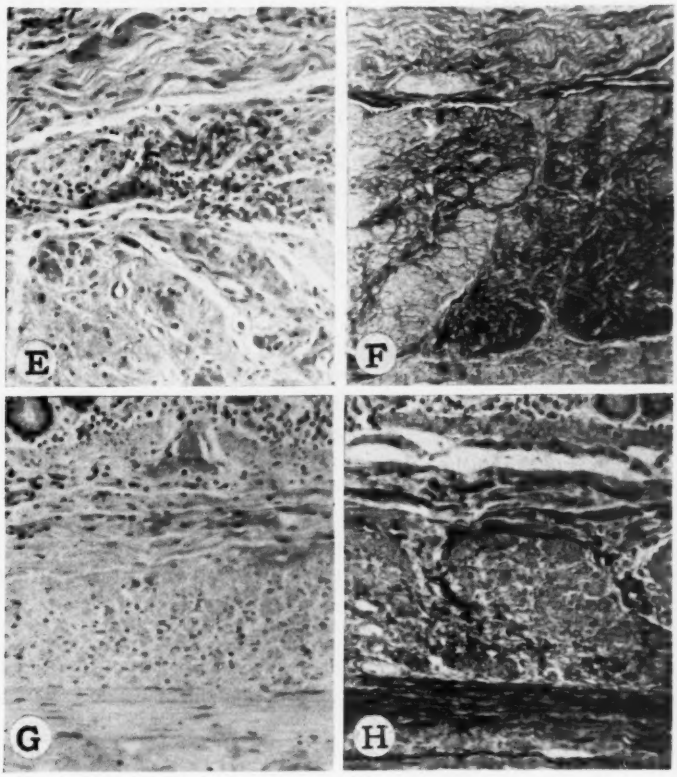


Fig. 3 (Continued).—*E*, esophagus, showing portions of the internal (above) and external layers of muscularis; few smooth muscle fibers in a condensed stroma; slight lymphocytic infiltration about nerve plexus. Hematoxylin and eosin; × 88. *F*, esophagus, showing entire external layer of muscularis and portion of internal layer (above); extensive loss of smooth muscle fibers; condensed fibroblastic stroma. Weigert-Van Gieson stain; × 30. *G*, jejunum, showing (from above downward) muscularis mucosae, submucosa, internal and external layers of muscularis; both layers of muscularis are narrow. Hematoxylin and eosin; × 88. *H*, jejunum, showing the same structures contained in *G*; the smooth muscle is replaced in part by elastic tissue. Weigert-Van Geison stain; × 88.

Roentgenologic Studies (Fig. 3).—Examination with barium showed some dilatation of the esophagus, with a slight decrease in peristalsis. The stomach was normal. Marked distention of the duodenum was noted, as well as of the proximal jejunal loops. Peristalsis was diminished. At four hours and at six hours the head of the barium meal had failed to progress significantly, and marked dilatation of all small bowel loops was present. On the basis of this examination,

the diagnosis of scleroderma was suggested.§ A barium enema showed evidence of sacculation of the transverse colon and inability to evacuate.

Roentgenograms of the hands showed calcific deposits in the soft tissues of the fingers.

Course.—The patient became progressively weaker, with intermittent nausea, vomiting, and diarrhea. An ulcer developed in her finger tip. Despite intensive general therapy and a course of corticotropin, she went progressively downhill and died about two months after entry.

Autopsy.—The autopsy was performed four hours after death. Most of the significant findings, aside from generalized atrophy of the organs, were in the alimentary tract. The lower half of the esophagus and the stomach were moderately dilated. The duodenum and rest of the small intestine were markedly dilated and thin-walled. The stomach contained about 1 liter of grayish fluid, and similar fluid filled the small intestine. The colon was not so strikingly dilated, and it contained semisolid feces. No mucosal lesions were found.

Histological examination showed a distinctive type of defect of the muscularis of the esophagus, stomach, and intestine. This consisted of scattered patches of extreme atrophy, or complete disappearance of muscle fibers, with shrinkage of the fasciculi and thickening of the interfibrillar framework. The remaining tissue stained like collagen in part, but there was a marked increase in elastic tissue in some lesions (Fig. 3*E, F, G, H*). The defect involved the inner circular layer of the muscularis in some places and the outer longitudinal layer elsewhere. Fibroblastic proliferation and inflammation were lacking, and the other layers were unaffected. Only a limited amount of tissue was saved for histological study; consequently, a systematic investigation of the extent of the lesions was not possible. There was a mild patchy scarring of the myocardium, and the right ventricular endocardium was thickened.

Comment.—This patient died of malnutrition. Her gastrointestinal symptoms were so severe and produced such debilitation that all efforts to augment her caloric intake failed to alter the course of her disease. A 10-day course of corticotropin did not affect her diarrhea, nausea and vomiting, and profound weakness.

Although she had no symptoms referable to her esophagus, there was roentgenographic evidence of diminished peristalsis. Small bowel changes were profound, with massive dilatation, both of the duodenum and of much of the remaining small bowel. The caliber of the loops was such as to suggest small bowel obstruction, of which there was no evidence, however, radiologically or on autopsy examination. Striking delay in motility was demonstrated. The nature and severity of the defects in the muscularis of the alimentary tract appear to afford an adequate basis for loss of tonus and peristalsis.

The flat curve following oral ingestion of glucose suggested interference with its absorption. There was, in addition, undigested food in the feces, in moderate quantities.

Skin manifestations were minimal and were overshadowed by the gastrointestinal involvement. The roentgenologic changes were so prominent that the diagnosis of scleroderma was suggested on the basis of the small bowel series, at a time when no clear-cut clinical diagnosis was apparent.

CASE 4 (292718).—A. S., a 37-year-old man, entered Stanford University Hospitals on Sept. 12, 1947, because of joint stiffness and epigastric distress of a few months' duration. He had been treated for syphilis with penicillin and bismuth in 1946, at about which time he had noted stiffness of the hands, shoulders, and hips. Meanwhile, he developed anorexia, weight loss, and generalized weakness and stiffness. His hands became sensitive to cold. Five months before admission he began to vomit, but a gastrointestinal series demonstrated no abnormalities. Three months before admission he developed epigastric distress, belching, and slight dysphagia. This persisted until admission.

§ Dr. William L. Anderson suggested this possibility.

Physical Examination.—The face was mask-like. The skin was strikingly smooth. There was limitation of motion in the fingers, and the extremities turned white on exposure to cold. The remainder of the examination was negative.

Laboratory Data.—Hemoglobin was 11 gm.; white blood cell count, 9,000, with normal differential count. Urine was normal. Results of the oral glucose-tolerance test were as follows: fasting, 77 mg. per 100 cc.; at one-half hour, 87 mg.; at one hour, 90 mg.; at two hours, 107 mg.; at three hours, 107 mg. The stool was formed, with moderate fat content, moderate vegetable cell content, and occasional undigested muscle fibers. Electrocardiogram showed widening of QRS complex and left axis deviation.

Biopsies of skin from the occipital region and of skin and muscle from the calf of the leg were made on Sept. 16, 1947. There were rather mild changes in the skin, consisting chiefly of pigmentation and increased thickness of the corium, judged compatible with scleroderma. There were widespread hyalinization and fragmentation of the skeletal muscle fibers, with focal mononuclear cell infiltration and foci of regenerating muscle fibers.

Course.—The patient was treated symptomatically, with some improvement. For two years, he felt significantly better and was able to do light work. Thereafter, he developed marked abdominal distention, with epigastric fullness and pain. In the recumbent position, he had regurgitation. He had increasing weakness and fatigue.

He reentered the hospital in September, 1949, markedly emaciated. He was treated symptomatically and was awaiting therapy with corticotropin when he developed abdominal pain, in November, 1949, and died.

Roentgenologic Studies (Fig. 4).—On the admission of September, 1947, no significant abnormalities were seen in the gastrointestinal tract or the chest. Two years later, in September, 1949, the esophagus showed diminished peristalsis. The stomach was normal, but there was dilatation of the duodenal loop. There was also marked dilatation of the remainder of the proximal small bowel. At two hours narrowed distal loops of ileum, and some remaining dilated proximal loops, with clumping and segmentation of the small bowel, were present. At six hours the head of the barium meal had reached the cecum but a large amount of barium remained in the small bowel loops, some of which were dilated.

Autopsy.—The autopsy was performed 12 hours after death. The heart was not enlarged, but the left ventricular endocardium was slightly thickened, and the myocardium contained small streaky scars. There was virtually no arteriosclerosis. The esophagus and stomach were not dilated. The duodenum was slightly dilated, and the rest of the small intestine was markedly dilated. The colon was of normal caliber. No mucosal lesions were seen. There were no other significant gross changes of the internal organs.

Histological examination showed patchy myocardial scarring and diffuse endocardial thickening of the left ventricle. There were focal atrophy and small mononuclear cell infiltrations of the skeletal muscle. Many sections from all parts of the alimentary tract showed diffuse atrophy of the muscularis. In addition to this, there were defects of the muscularis of the esophagus like those described in Case 3 (Fig. 4*E* and *F*). Moreover, there was extensive replacement of smooth muscle fibers by a similar fibroelastic tissue in the urinary bladder.

Comment.—This patient, like the last, was markedly wasted and malnourished when death occurred. His symptoms had been progressive over a two-year period, with gradual marked weight loss resulting. Dysphagia was never a prominent symptom and, roentgenologically, the changes in the esophagus were minimal. Abdominal distention, epigastric distress, nausea, and vomiting dominated the clinical picture. Initially his gastrointestinal studies were negative, but two years later there were marked changes in the small bowel. At autopsy, one month after the final gastrointestinal examination, there was gross dilatation of the small bowel, particularly marked in the jejunum. No evidence of intestinal obstruction was seen.

As in Case 3, a flat glucose-tolerance curve was present. Failure of the blood sugar to rise above 107 mg. per 100 cc. again suggests that the glucose was being absorbed very slowly from the small intestine.

CASE 5 (302747).—B. A., a 44-year-old woman, entered Stanford University Hospitals on Sept. 20, 1950, because of sore fingers and epigastric distress. At the age of 25 she had noted that her fingers turned blue on exposure to cold. She first had occasional epigastric pain, easy fatigability, and tanning of the skin of her arms and face about eight years before admission. Her skin gradually became tight and thickened, with increasing bronzing and impaired flexion

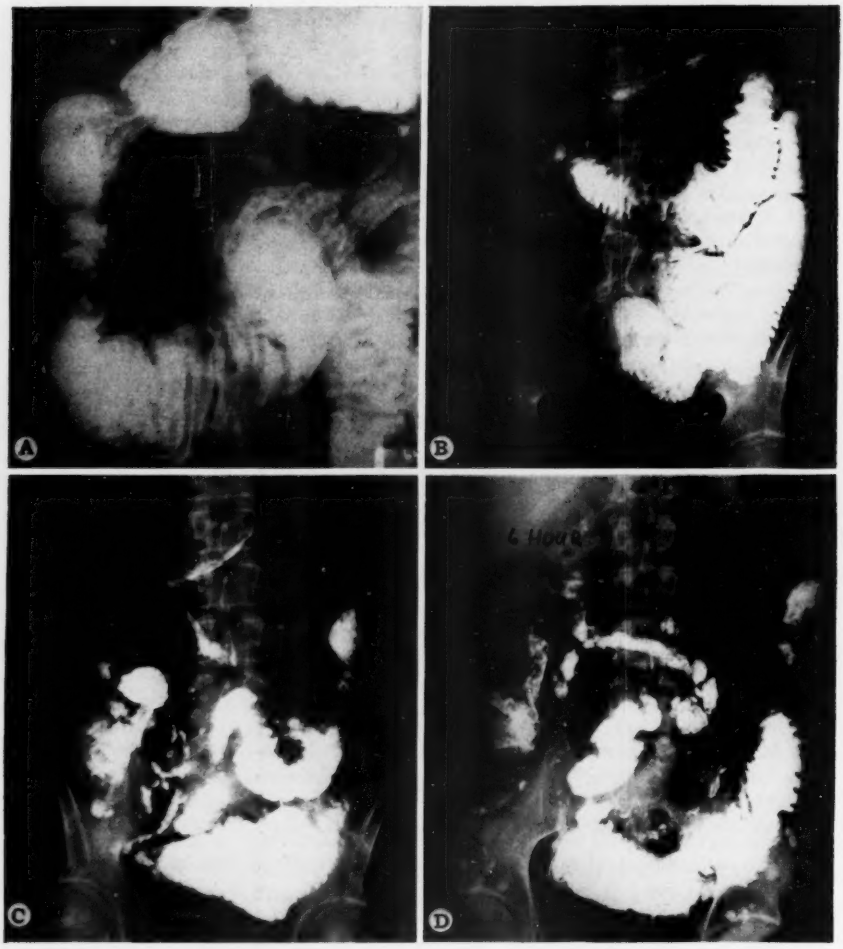


Fig. 4 (Case 4).—Scleroderma. Gastrointestinal series. *A*, immediate film: Note the dilated duodenum and proximal jejunum. *B*, one-hour film: There is marked dilatation of jejunal loops. *C*, two-hour film: Dilated jejunal loops have partially emptied; some dilated small bowel loops are present in the pelvis; distal ileal loops are narrow and irregular. *D*, six-hour film: There has been little progress of the barium column; most of the barium remains in dilated mid-small-bowel loops, and some discontinuity of the barium column is present.

of her fingers. She developed swelling in her digits, which occasionally drained or were incised, with removal of coarse granular calcific material. Recently, bloating, intermittent cramping abdominal pain, and nausea and vomiting had become prominent.

Physical Examination.—There was bronzing of the patient's entire body, more marked over arms, neck, and face. Her skin was smooth and taut. There were healed ulcers on the tips of her fingers, hard nodules beneath the skin of the right calf and left thigh, and small ulcerations on the plantar surfaces of both great toes. The remainder of the examination was not significant.

Biopsy of the skin was performed on Sept. 24, 1950. It showed changes compatible with scleroderma, consisting chiefly of increased thickness of the corium and penetration of the subcutaneous adipose tissue by broad collagenous septa.

Course.—The patient was started on corticotropin, 100 to 150 mg. daily for five days, 60 to 80 mg. daily for the next two weeks, and thereafter 40 mg. daily for the succeeding four months. There was striking improvement in the condition of her skin, which became looser and pinker. She had increased mobility of her extremities, and the Raynaud syndrome almost entirely disappeared. Her gastrointestinal symptoms, however, were not diminished. At the end of five months, she was placed on cortisone, 100 mg. daily. This produced aggravation of her gastrointestinal symptoms, and the dose of cortisone was gradually reduced to 40 mg. daily. In spite of this, there were increasing abdominal distention and epigastric pain, and, finally, after three and one-half months, cortisone was discontinued and corticotropin was started again. There was some improvement, and her gastrointestinal symptoms were not so marked during the next

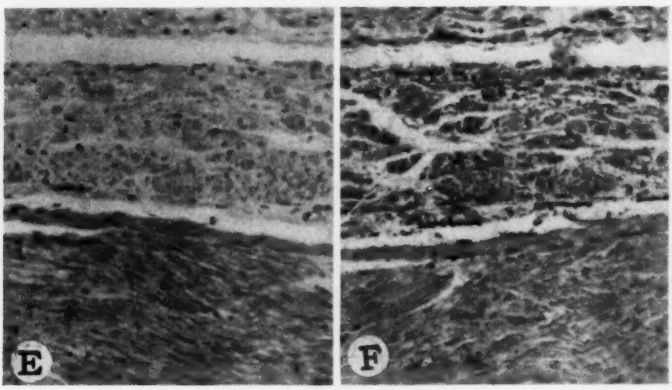


Fig. 4 (Continued).—*E,* esophagus, showing the entire internal (above) and part of the external layer of musclularis: the latter appears normal but the former contains few smooth muscle fibers in a condensed stroma. Hematoxylin and eosin; × 88. *F,* esophagus, showing the same structures contained in *E;* the smooth muscle of the internal muscular layer (above) is partially replaced by elastic tissue. Weigert-Van Gieson stain; × 88.

month of corticotropin therapy, but, because it seemed to be having no further effect, corticotropin was discontinued. Within three months, skin and joint stiffness returned. Thus, this patient had a nine-month trial, from September, 1950, to July, 1951, of both corticotropin and cortisone, with definite improvement in her skin and joints but not in her gastrointestinal symptoms. During the past year and one-half there has been steady deterioration of her condition, with increasing abdominal distress, anorexia, and profound malnutrition.

Roentgenologic Studies (Fig. 5).—In 1950 there was almost complete absence of peristalsis in the esophagus, but the remainder of the gastrointestinal tract was essentially normal. In 1951 there was dilatation of the duodenum and marked dilatation as well of some of the jejunal loops. The most recent gastrointestinal series, performed in 1953, showed some alteration of mucosal pattern, dilatation, and delayed transit time of the barium.

Comment.—Although this patient had classical cutaneous manifestations of scleroderma for many years, the marked visceral involvement was of relatively recent onset. The most troublesome symptoms were epigastric distress and "bloating." With corticotropin therapy, her skin and joints responded well but the gastrointes-

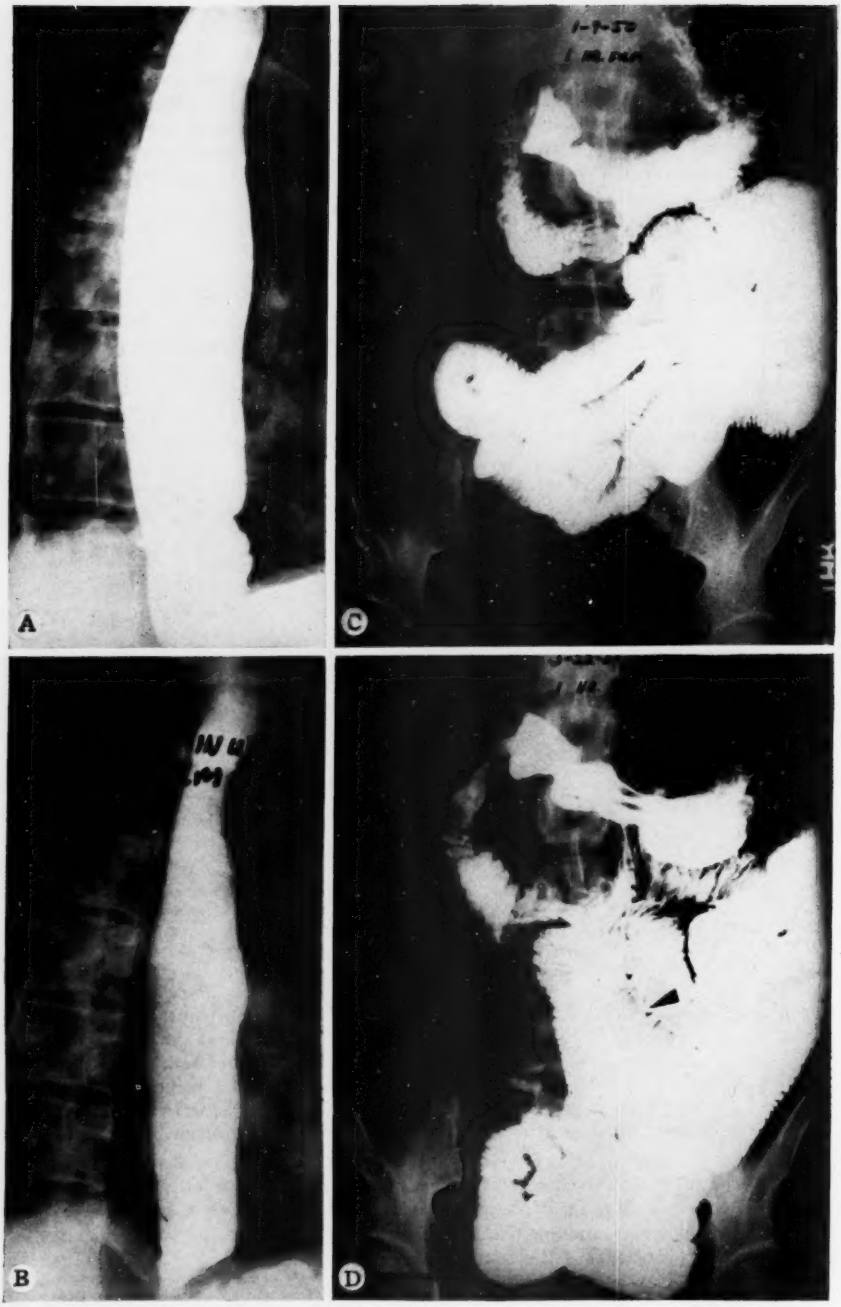


Fig. 5 (Case 5).—Scleroderma, *A*, esophagus. Immediate film: At fluoroscopy, the esophagus was dilated and peristalsis markedly diminished. *B*, esophagus. Ten-minute film: A large amount of barium remains in the dilated esophagus. *C*, gastrointestinal series, Jan. 9, 1950. One-hour film: There is slight dilatation of the third portion of the duodenum; the jejunal loops are at the upper limits of normal size. *D*, gastrointestinal series, March 22, 1951. One-hour film: The duodenum is dilated; marked dilatation of some jejunal loops is apparent (arrows).

tinal symptoms persisted. Cortisone seemed to aggravate the abdominal symptoms. When it became apparent that corticotropin and cortisone were no longer helping her, they were discontinued. With symptomatic therapy, her progressive downhill course has continued.

A striking finding was the dilatation of the small bowel present on the examination of March 22, 1951. Two years later marked delay in transit time had become evident.

As in the previous two patients, esophageal changes were demonstrated roentgenologically but there were no symptoms referable to the esophagus. A significant residue of barium was present in the esophagus 10 minutes after its ingestion.

CASE 6 (298596).—A. T., a 52-year-old white housewife, entered Stanford University Hospitals on April 24, 1950, because of painful fingers and toes, dysphagia, and abdominal bloating. Seven years earlier she had noted that her fingers became painful, cold, and blue during periods of emotional upset or on exposure to cold. Tightness and thickness of her skin developed, and subsequently lumps appeared on her forearms which, on excision, were found to contain calcium. At the time of onset of the pain in her fingers she also noted difficulty in swallowing solid food. This gradually increased. She also had marked abdominal bloating and significant weight loss for one year prior to admission. A moderate hypertension was recorded.

Physical Examination.—The patient was thin and looked older than her age. The skin of her hands and feet was thickened and had the classical appearance of scleroderma. There were nontender subcutaneous nodules over the volar surfaces of both forearms. Scars of old ulcerations on her left great toe were noted. The facial expression was fixed. Auscultation of the heart revealed numerous premature beats but no murmurs. The lungs were clear. The abdomen was markedly distended.

Laboratory Data.—Noncontributory. Electrocardiogram showed auricular premature beats, abnormal T-waves, and low voltage QRS complexes.

Biopsies of the skin of the thigh and dorsum of the foot and of the vastus medialis muscle were performed on April 27, 1950. The muscle was normal. The skin was unremarkable except for slight thickening of the corium, as judged by the incorporation within it of deep-seated sweat glands.

Course.—The patient was started on cortisone therapy, and there was evidence of improvement in the skin, the swallowing, and the abdominal distention. After three weeks, however, she became psychotic and cortisone therapy was discontinued. She was followed on the outside, without significant change in her dysphagia or abdominal distention. She developed nausea and vomiting and, finally, dyspnea. In October, 1950, her symptoms became worse and she died.

Roentgenologic Studies ‖ (Fig. 6).—Upper gastrointestinal series performed elsewhere on March 9, 1948, showed diminished esophageal peristalsis, esophagitis with esophageal ulcer in the distal esophagus, and an abnormal small bowel pattern. There was marked narrowing of some loops of small bowel, with dilatation of others, clumping, irregularity of progression, and delayed motility. On Dec. 12, 1949, dilatation of the distal third of the duodenum and much of the small bowel was present. On April 26, 1950, there were similar findings, with rather striking delay in motility. The mucosal pattern appeared somewhat irregular in many loops. On May 17, 1950, marked dilatation of the duodenum and of multiple small bowel loops was noted. At eight hours the head of the barium meal had failed to reach the colon, and much of the barium remained in the proximal small bowel. When barium finally reached the terminal ileum, it too was significantly dilated. Barium enema showed a markedly dilated, atonic colon.

Multiple calcific deposits in the soft tissues of the forearms and hands were also demonstrated.

Autopsy.¶—Autopsy showed the most significant abnormalities in the cardiovascular system and the alimentary tract. The heart was very small, as were the other organs, but there was

‖ Dr. Henry Brean allowed us to study some of the roentgen examinations on this patient.

¶ Dr. H. R. Fishback provided a transcript of the autopsy protocol and allowed us to review the histological sections.

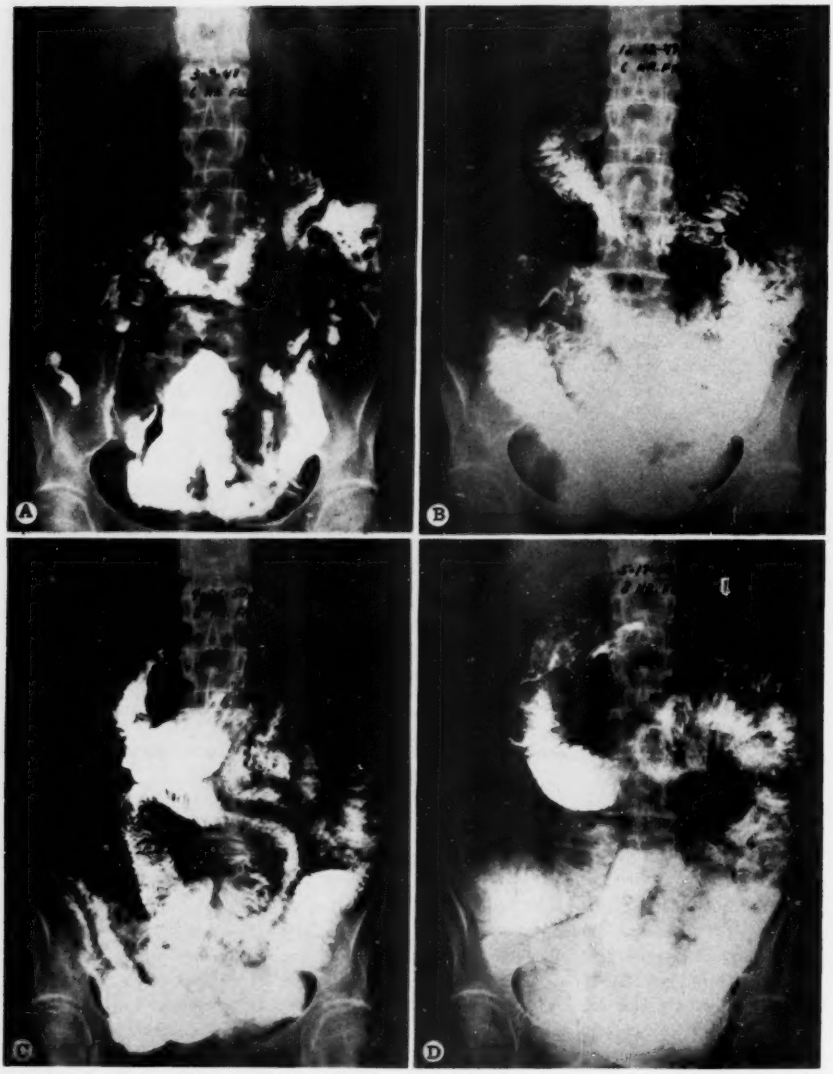


Fig. 6 (Case 6).—Scleroderma. *A*, gastrointestinal series, March 9, 1948. Six-hour film: There is marked discontinuity of the barium column; dilated areas alternate with the long narrow segments; the second portion of the duodenum is slightly dilated; motility is impaired. *B*, gastrointestinal series, Dec. 12, 1949. Six-hour film: The third portion of the duodenum is dilated, as is much of the small intestine; the narrowed areas previously seen are no longer present one year later. *C*, gastrointestinal series, April 26, 1950. Eight-hour film: Barium has not yet filled the cecum; dilated segments are apparent, together with some areas of normal caliber; the mucosal pattern is normal. *D*, gastrointestinal series, May 17, 1950. Eight-hour film: Gross dilatation of the third portion of the duodenum and most of the small intestine is present; the head of the barium meal remains in the small bowel.

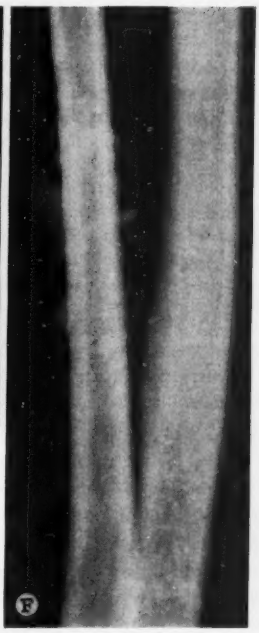
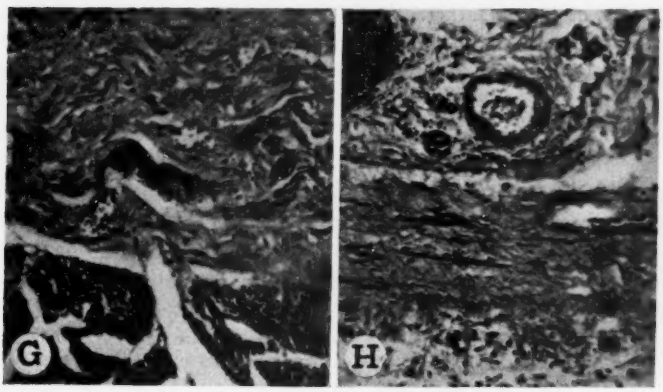


Fig. 6. (Continued).—*E*, esophagus. The proximal esophagus is dilated; an ulcer (verified at autopsy) is present in the distal esophagus. *F*, forearm. There is extensive calcification in the subcutaneous tissues.



G, esophagus, showing portions of the internal (above) and external layers of muscularis. There is extensive loss of smooth muscle fibers from the internal layer. Phosphotungstic acid hematoxylin; × 100. *H*, colon, showing portion of submucosa (above) and entire muscularis. The latter is a narrow condensed fibroelastic layer in which rare, thin, smooth muscle fibers persist. Phosphotungstic acid hematoxylin; × 100.

massive scarring of the apex of the left ventricle and ventricular septum. There was severe coronary arteriosclerosis, with occlusion of the left anterior descending branch by a thrombus at a point of aneurysmal dilatation. There was also severe generalized arteriosclerosis, with a thrombosed aneurysm of an iliac artery. The right kidney was extremely shrunken and scarred.

The esophagus was moderately dilated in its proximal two-thirds. There was a small diverticulum of the anterior wall in the middle third. The distal third was described as markedly thickened by a gray-white fibrous tissue, with irregular roughening of the lining, and a superficially eroded area with a "meaty," granular surface was found near the cardia. The stomach was small and pliable, with normal rugae. The small intestine is said to have appeared normal. The ascending and transverse colon were greatly distended with feces, and multiple scattered areas of superficial ulceration of the mucosa were found throughout the dilated segment. The descending colon appeared normal.

Histological examination showed defects of the muscularis of the esophagus and colon (Fig. 6*E* and *F*) essentially identical to those in Cases 3 and 4. No sections of the stomach and small intestine were obtained. There was also a chronic ulcer of the lower end of the esophagus, with scarring of its base and neighboring chronic inflammation of the wall. A section was also made of a small acute ulcer of the colon, which was superficial. It is noteworthy that this latter ulceration occurred in a segment where the entire muscularis was reduced to a thin layer of fibroelastic tissue. However, the muscular defect extended far beyond the limited area of inflammation about the ulcer, and the muscular defect in the esophagus also was far removed from the area of inflammation and ulceration. The myocardial scarring was associated with severe coronary arteriosclerosis.

Comment.—The Raynaud phenomenon and dysphagia first occurred six years before the onset of abdominal bloating and roentgenologic evidence of bowel involvement. The esophagitis was marked and was an important element in the development of inanition. The abdominal distress and bloating were also prominent features clinically, particularly in the later stages of the disease.

On cortisone, there was an immediate subjective response, with better appetite and improvement in swallowing. The development of a psychotic episode forced discontinuation of cortisone therapy. This was the only case in the series in which a definite esophageal ulcer was demonstrated. Serial small bowel examinations, over a four-year period, showed progressive changes in the appearance of the intestine. A limited histological examination showed severe defects of the muscularis, like those in Cases 3 and 4.

GENERAL COMMENT

Perhaps the most striking aspect of these cases is the evidence that scleroderma with intestinal involvement can at times be a rapidly progressive fatal disease. Three of the cases were of relatively long duration, and the development of visceral symptoms, other than dysphagia, was late. In the other three, the course was far more rapid, two dying within two years after the onset of the disease. In this second group, dysphagia was a later manifestation than abdominal pain or distress, anorexia, nausea, and vomiting, and in one case dysphagia was entirely absent. The onset of epigastric distress was accompanied by anorexia, and thereafter weight loss and inanition developed. Skin changes were present in all patients, the type of change varying with the stage of the disease. There was no correlation between the extent of skin change or skeletal disability and the degree of intestinal involvement. In one case the appearance of the skin was an insignificant feature and failed to suggest the diagnosis. All six patients had the Raynaud phenomenon, and in three it marked the onset of the disease. In general, no significant clinical evidence of pulmonary involvement was present. Two of the autopsied cases had myocardial scarring without associated coronary arteriosclerosis.

Although high blood calcium levels have been noticed occasionally in scleroderma, there was no evidence in these cases of disturbed calcium metabolism. The most interesting laboratory finding was the demonstration in two patients, those with the most rapid course, of a flat glucose-tolerance curve. The very slow rise, in four hours from 62 to 80 mg. per 100 cc. in Case 3 and in three hours from 77 to 107 mg. per 100 cc. in Case 4, suggested that glucose was not being normally absorbed. Perhaps the absence of normal mixing and decreased contact between the intestinal wall and the bowel contents, based on diminished peristalsis, was responsible. No evidence of significant liver, pancreatic, or any other disease which might offer an alternate explanation was found. Flat glucose-tolerance curves have also been described in sprue and other nutritional disorders in which there is impaired absorption.[23]

Roentgenologically, the most striking abnormality in the small bowel was a marked dilatation. The bolus of barium entered the involved loop and distended it to two or three times its normal size. Although the bolus should have been an effective stimulus for peristaltic waves, peristalsis either did not occur or was of diminished amplitude, and the bowel remained distended for a considerable period of time. Similar abnormalities are present in the esophagus in scleroderma. Contractions are diminished or absent, and gravity must frequently be relied upon for the bolus to reach the stomach. A balloon placed in the esophagus demonstrates slow or absent propulsion and decreased tone,[24] and it seems likely that balloon studies of the small bowel might reveal identical findings. Esophagitis (Case 1) or peptic ulcer of the esophagus (Case 6) are found not infrequently, but they are not primary manifestations of the disease. They are probably caused by regurgitation of acid gastric secretions through a patulous esophagogastric junction, with subsequent development of an inflammatory reaction.[2]

The size of some small bowel loops was such as to suggest intestinal obstruction. The normal diameter of the jejunum is 2 to 3 cm., but in all of our cases, except one, loops with a diameter of 5 cm. or more were demonstrable. In some cases the dilatation was quite localized, while in others it involved large portions of the small bowel. The proximal small bowel showed far greater evidence of involvement than the ileum, although in two of our cases significant dilatation of the ileum was present. Dilatation may be limited to the duodenum (Case 1) and, if so, usually ends about 4 to 5 cm. before the ligament of Treitz. This was a remarkable feature in some of the collected cases.

Hypomotility was present in all but one of our cases (Case 1). Normally, the head of the barium meal may be expected to reach the cecum in 2 to 4 hours.[25] In some of our cases, the barium failed to reach the cecum by 8, 10, or even 12 hours. The reason for this delay almost certainly lay in the inability of involved portions of the bowel wall to respond to the normal stimulus for peristalsis.

Even in the presence of profuse diarrhea, transit time was markedly prolonged (Case 3). This, however, is not entirely unexpected, since impaired motility has been demonstrated in acute dysentery.[26]

In a few instances the mucosal pattern appeared abnormal, but this was not a prominent finding. Segmentation of the barium, similar to that seen in sprue or some of the hypovitaminoses, was occasionally encountered. For the most part, however, there was continuity of the barium column. In Case 6, in which follow-up

films were obtained over a period of three years, it was striking that on the first examination there appeared to be narrowing of the small bowel and segmentation of the barium. A year later there was significant dilatation. Duodenal stasis increased over a two-to three-year period. The valvulae were sharp and clearly delineated. On the final examination prior to death, the entire small bowel, including the ileum, was dilated, without significant discontinuity (Fig. 6). Thus, the small bowel findings may be distinctive in the full-blown picture and should be distinguished from those of the so-called "motor dysfunction pattern." The degree of dilatation seen in scleroderma is rarely encountered in the deficiency pattern. Involvement of the third portion of the duodenum is a prominent feature of scleroderma, as is the frequent localization of findings to proximal small bowel loops. In the motor dysfunction pattern, the mid small bowel is commonly the site of some of the most typical findings.[25] Segmentation, spasm, flocculation, and disturbance of contour, while present occasionally in scleroderma, were not prominent features in our cases.

Rarely, other diseases may produce a similar roentgenologic appearance. We have seen one case each of amyloid and of leukemic infiltration of the small bowel, with segmental destruction of the muscularis and associated marked dilatation of small bowel loops. Paralytic ileus and mechanical small bowel obstruction must also be considered.

Sacculation of the colon, similar to that in Case 3, has received recent emphasis in the literature [31]; the colon may also be large, atonic, and incapable of proper evacuation.

In the three cases autopsied there was more or less dilatation of various segments of the alimentary tract. This was particularly marked in the esophagus in two cases (Cases 3 and 6) and in the small intestine in two cases (Cases 3 and 4). The small intestin dilatation involved the duodenum conspicuously in Case 3. It was marked in the colon only in Case 6 and only in this case was there ulceration and scarring of the distal third of the esophagus. No cause for a mechanical obstruction was demonstrated in any case, excepting possibly the esophageal scarring and ulceration in Case 6. It seems clear from a consideration of these findings and of the findings in other reported cases in the literature that the dilatation and motor disturbances demonstrated in the alimentary tract in this disease are intrinsic in origin and adynamic in nature. The distinctive histological defect in the muscularis affords a convincing basis for such disturbances. The loss of muscle fibers is the predominant change; by comparison, the fibrosis appears very mild. The extent of this alteration is not disclosed by this study, since a sufficient sampling of the tract has not been made in every case. However, in the whole group it has been shown to occur patchily in all segments from the esophagus to the colon. In one case an identical type of muscular defect has been shown in the urinary bladder; this may reflect a systemic affection of smooth muscle. The lesions referred to are undoubtedly of the same nature as those described and illustrated by Bevans [9] (in two cases of scleroderma in which clinical evidence of disturbed alimentary function was observed). It is probable that the lesions described in two cases of Matsui,[27] in one case of Goetz,# and in one case of Spain and Thomas [28] were of the same character.

References 13 and 14.

Others * also have reported atrophy of the intestinal muscularis, without sufficiently detailed descriptions or illustrations to enable one to make a strict comparison with the lesions in these cases.

The main elements of therapeutic interest in these cases were the effects of corticotropin and cortisone. All other agents employed have been thoroughly reviewed in the literature.[31] In Case 2, cortisone produced a prompt and dramatic response, both objective and subjective. The skin became less tense and the joints less stiff. Appetite, weight, and strength increased. Abdominal symptoms were improved. That part of this may have been due to the general effect of the drug rather than a specific effect on the disease is suggested by the development of euphoria, which, after four months, prompted the substitution of corticotropin for cortisone. On corticotropin therapy the patient maintained her improvement for about eight months, at the end of which time symptoms returned and cortisone therapy was reinstituted. Improvement again followed, maintained for the past one and one-half years on 35 mg. of cortisone daily. No signs of toxicity developed. Whether this amount of cortisone is actually responsible for her present state of good health or whether therapy initiated a remission which has been self-sustained is uncertain.

The use of corticotropin in Case 3 came so late in the course of the disease that its failure to alter the downward course is probably of no significance.

In Case 5 the initial excellent response to corticotropin in terms of skin, joints, and the Raynaud phenomenon was not accompanied by amelioration of epigastric distress or distention. Cortisone actually aggravated the gastrointestinal symptoms, without altering the cutaneous manifestation. Readministration of corticotropin produced no significant effect, and the patient is now in so marked a state of malnutrition that she will probably die soon.

Finally, Case 6 demonstrated an encouraging initial response to cortisone, which could not be further investigated because of the development of a psychotic episode.

Thus, both cortisone and corticotropin were effective in producing temporary relief, and in one patient a sustained remission was initiated. These findings accord with previously published results, which emphasize the immediate response and the failure to alter permanently the course of the disease.† The possible dangers of cortisone treatment have also been stressed.[36] In only one of our cases was there evidence that the course of the intestinal involvement was influenced.

SUMMARY

The entire alimentary tract may be involved in scleroderma, causing progressive interference with nutrition and, at times, death. Clinical symptoms may be accompanied by significant radiologic changes in peristalsis, motility, tonus, and caliber, which appear to be explicable by a distinctive structural defect in the muscularis of the alimentary tract. Six illustrative cases have been reported in detail, and the clinical, radiological, and pathologic features of intestinal involvement have been described.

* References 16, 29, and 30.

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PSITTACOSIS

Report of Seven Cases

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THE INCREASING popularity of parakeets as domestic pets, the lack of uniform laws regarding the importation and sale of psittacine birds, and the presence of a large reservoir of the disease among domestic fowl have increased the incidence of psittacosis tremendously. Since Ritter first described the disease under the name of pneumotyphus, psittacosis has been reported as endemic or epidemic in many parts of the world. Any attempt to determine the true incidence of the disease is futile. It is certain that psittacosis occurs much more frequently than is generally realized. That it is overlooked because of the unawareness of the medical profession of its existence is most likely.

Psittacosis is an acute infectious disease caused by a number of closely related viruses. In addition to the strains of psittacine origin, there are various other strains which naturally infect other species of birds. These latter infections are referred to as ornithosis. The disease is transmitted to man primarily from infected birds. The illness is characterized by a febrile course with pneumonic changes of a diffuse interstitial nature. Since the advent of antibiotic therapy the case fatality rate of the disease has decreased from 50% to approximately 2%.

The following seven cases * encountered in the past three years form the basis for this report and for a discussion of the psittacosis problem.

REPORT OF CASES

CASE 1.—M. T., a 54-year-old woman, was hospitalized on Oct. 23 because of a febrile illness with cough and generalized aching of two days' duration. Examination of the chest revealed scattered moist rales with harsh breath sounds in the right pulmonary base and the left midlung field. The temperature was 102 F.; the pulse rate was 116 per minute, and the respiratory rate was 26 per minute. The blood pressure was 164/102. Fever (temperature to 102 F.) was present for one week, despite the daily administration of 300,000 units of penicillin procaine intramuscularly. There was gradual clearing of the rales in both lung fields, and the cough and arthralgia disappeared. The patient was discharged from the hospital on Nov. 2.

Cleo Roberts, B.S., gave technical assistance.

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* Drs. Charles Beck, Morris Lev, Phillip Lewin, Sidney Portis, and S. Marks gave us permission to study their cases.

Chest x-ray showed areas of increased density in the right base and in the left midlung field suggestive of pneumonitis. Results of urinalysis were normal. The blood Kahn test was negative. No definitive diagnostic procedures were done.

A presumptive diagnosis of psittacosis was made because of the patient's occupation, as the manager of the pet section of a large department store. Parakeets were sold, but the patient denied the presence of any sick birds in the store. Shortly after her discharge she returned to her previous occupation.

Thirteen months later, on Dec. 23, she noted fever, generalized aching of the extremities and of the back, and severe headache. Medical care was not sought until Dec. 26, at which time her temperature was 103 F. Scattered moist rales were noted in the right pulmonary base; otherwise examination was not remarkable. The patient refused hospitalization, and therapy at home was undertaken. Penicillin, 300,000 units, intramuscularly, was given daily for three days with no drop in temperature. Temperature of 103.6 F. was present on Dec. 29. The patient appeared very toxic, and she complained of great discomfort in the chest and of general discomfort. On this day chlortetracycline (Aureomycin) therapy, 500 mg. every four hours, was instituted. Within 24 hours the temperature had fallen to 99.4 F., and the patient felt symptomatically improved. The dosage of chlortetracycline was reduced to 250 mg. every four hours. On Jan. 3 the patient was afebrile and examination of the chest showed no abnormalities.

A chest x-ray was taken on Jan. 10 and was reported to be negative for pulmonary pathology.

Blood obtained Jan. 3 was tested for complement-fixing antibodies of the psittacosis-lymphogranuloma venereum group and was reported positive in a dilution of 1 : 20.

Despite strong urging that she seek employment elsewhere, the patient returned to her previous occupation. No further follow-up of this case has been possible.

CASE 2.—E. W., a 45-year-old woman, was hospitalized on Nov. 30 because of pleuritic pain which had begun 10 days prior to admission. Anorexia and weight loss of 10 lb. (4.5 kg.) had been present in the two weeks prior to admission. She had not noted fever, but chills were experienced the day of admission. Past history was not significant.

Examination on admission revealed a blood pressure of 130/82, temperature 99.4 F., pulse rate 76 per minute, and respiratory rate 20 per minute; the respirations were grunting and shallow. There was decreased fremitus in the base of the left lung; percussion revealed dullness in the right base; occasional inspiratory wheezes were present in both lung fields, and a few fine moist rales were heard in the right base. There was a soft apical systolic cardiac murmur; the heart size was within normal limits.

The patient's course in the hospital was uneventful. The temperature fell to normal the day after admission and remained so for the duration of her hospital stay. She continued to complain of pain in the right chest throughout the time she was in the hospital. Examination on Dec. 13 showed no evidence of pulmonary abnormality. Treatment consisted of penicillin procaine, 300,000 units intramuscularly given daily for the entire length of her hospital stay.

Chest x-ray on Dec. 6 showed blunting of the right costophrenic angle, with minimal effusion in the right base; the other intrathoracic structures were within normal limits. Urinalysis and blood chemistry were not significant. The Kahn test was negative.

Blood was examined for complement-fixing antibodies against the psittacosis-lymphogranuloma venereum group on Dec. 7 and was negative. Blood serum drawn on Dec. 20 was positive in 1 : 32 dilution.

The patient worked in a pet shop where several parrots had died three and four weeks prior to her illness.

CASE 3.—L. H., a 31-year-old woman, was hospitalized on March 2 because of a febrile illness, which began on Feb. 28 with stiff painful neck and back, severe leg pains, and temperature of 105 F. She was seen by a physician the night her illness began and was given an injection of penicillin. The following day a nonproductive cough with mild dyspnea, but no chest pain, was noted. Past history was noncontributory.

Temperature on admission was 100.8 F., with pulse rate of 88 per minute and respiratory rate of 22 per minute. There was limitation of motion of the neck in all directions, but there was no rigidity. Examination of the chest revealed dullness in the left pulmonary base, with bronchovesicular breathing and diffuse inspiratory rales therein. Treatment, consisting of peni-

cillin procaine, 400,000 units intramuscularly daily, and chlortetracycline, 500 mg. twice daily, was begun on admission. On March 3 the patient was afebrile and the chest was normal on auscultation. She was discharged on March 6.

Chest x-ray on March 6 was essentially normal. Urinalysis was negative. The sedimentation rate was 16 mm. in an hour (Wintrobe). The Kahn test was negative, as were the cold and Streptococcus MG agglutination tests. The absorbed heterophile antibody agglutination test was positive in 1 : 10 dilution. The psittacosis-lymphogranuloma venereum complement-fixation test was positive in dilution of 1 : 256.

The patient lived where a parakeet was kept as a pet. The bird was not ill nor was there any similar illness among the other inhabitants of the house.

Case 4.—L. H., a 63-year-old woman, was admitted on Feb. 25 for arthrodesis of a Charcot deformity of the right knee. Surgery was performed on March 5. The postoperative course was uneventful until March 19, at which time a nonproductive cough with burning chest pain began. On March 20 the patient suddenly experienced nausea and emesis and her temperature rose to 102.8 F.

Examination showed a mildly congested pharnyx and scattered subcrepitant rales in the lower half of both lungs posteriorly. The remainder of the examination was noncontributory.

The patient had been placed on penicillin, 400,000 units intramuscularly daily, on March 5, the date of surgery. Chlortetracycline, 250 mg. every six hours, was administered from March 10 to March 14. When fever began, on March 20, chlortetracycline in a dosage of 500 mg. every six hours was restarted. There were rapid subsidence of fever and general improvement. Clearing of the pulmonary involvement occurred within two days after initiation of chlortetracycline therapy. The patient was discharged on April 1.

Chest x-ray on March 21 showed moderate elevation of the right diaphragm and diffuse exaggeration of the bronchovascular markings, especially in the right base. On March 23 another x-ray was unchanged except for some increase in the basal bronchovascular markings; no pneumonitis could be definitely identified.

The Kahn test was 4 +. The complement-fixation titer for the psittacosis-lymphogranuloma venereum group on March 21 was 1 : 5, and when repeated, on March 27, it was 1 : 20.

This patient shared a two-bed room with the patient of Case 3.

Case 5.—J. O., a 65-year-old man, was admitted on Dec. 26 because of acute, severe pain across the anterior chest, which had begun the previous night. The pain was intensified by movement and by deep breathing. There was an associated marked weakness. The patient had been treated for cardiac failure of a mild degree for the past three years.

On admission the temperature was 99 F.; the pulse rate was 110 per minute, and the respiratory rate was 22 per minute. Dullness and subcrepitant rales were present in the left pulmonary base. There was moderate cardiac enlargement. The blood pressure was 180/85; no cardiac murmurs were present. The remainder of the examination was essentially normal. Oxytetracycline (Terramycin), 250 mg. every six hours, was begun on admission and was continued to Jan. 4. At this time all specific medication was discontinued. On Dec. 27 the temperature rose to 100 F., and then it fell to 99 F. for the next two days. On Dec. 30 the temperature rose to 101 F., after which it fell to normal and remained there for the duration of the patient's hospitalization. The physical findings of pneumonic involvement gradually disappeared. On Jan. 12 the chest was entirely clear to examination. The patient was discharged from the hospital on Jan. 18.

Chest x-ray taken on Dec. 28 revealed the heart to be moderately enlarged to the left, and the aorta was elongated; there was moderate exaggeration of the bronchovascular markings, but no evidence of pulmonary consolidation was noted.

A second chest x-ray, taken on Dec. 31, showed an area of pneumonitis in the left base immediately above the diaphragm and partially obscuring it. Chest x-ray taken on Jan. 9 showed exaggerated bronchovascular markings throughout both lung fields but no evident parenchymal infiltration.

Sputum culture Dec. 31 revealed normal throat flora.

The psittacosis-lymphogranuloma venereum complement-fixation test, performed on Jan. 8, was positive in a dilution of 1 : 32, and when repeated, on Jan. 14, it was positive in 1 : 128

dilution. The patient owned a canary and had been exposed to parakeets when he went to a pet shop to purchase seed for his canary. Two weeks prior to the onset of his present illness he had attended a pigeon show.

CASE 6.—R. G., a 52-year-old woman, was hospitalized on Nov. 18 because of headache, chest pain, sore throat, and cough productive of small amounts of blood-tinged sputum and general malaise of seven days' duration. Fever had been present for four days prior to admission. Past history was insignificant except for diabetes mellitus, which was controlled by diet only.

Examination revealed temperature of 103 F. and a pulse rate of 100 per minute. The chest was resonant to percussion throughout. There was bronchovesicular breathing, and coarse rales were present in the left pulmonary base. Therapy consisted of oxytetracycline, 250 mg. every four hours for the first five days, after which the dosage was reduced to 250 mg. every six hours. The temperature returned to normal by the third hospital day. The physical findings in the chest cleared on the sixth day. The patient was discharged on Nov. 30.

Chest x-ray, taken on Nov. 19, revealed a diffuse veil-like density throughout the lower half of the left lung. The x-ray was repeated on Nov. 26, and almost complete clearing of the density was observed. Sputum examination for tubercle bacilli was negative on three specimens. Urinalysis and blood chemistry examinations were not significant.

Psittacosis-lymphogranuloma venereum complement-fixation test on Nov. 22 was positive in a dilution of 1 : 64. This was repeated on Nov. 30 and was positive in a dilution of 1 : 256.

The patient was the manager of a pet shop. Approximately 10 days prior to the onset of her illness she had received a shipment of parrots, all of which appeared to be well.

CASE 7.—J. A., a 68-year-old man, was admitted on Sept. 21 with the complaint of fever. The fever had been intermittently present for six months prior to admission. It came on every two to three weeks and was accompanied by shaking chills and sweats. The temperature was elevated from 102 to 103 F. on at least 12 occasions. The patient was otherwise well and had not received any therapy. His past history included dyspnea on mild exertion and intermittent episodes of paroxysmal nocturnal dyspnea.

Examination revealed an obviously dyspneic elderly man with a temperature of 100.8 F., pulse rate of 110 per minute, and blood pressure of 178/112. The chest was resonant; many rales were heard over the left lower lung field, and a few were heard at the right base. The cardiac apex was in the fifth interspace just lateral to the midclavicular line; the rhythm was sinus, with frequent premature beats, and a gallop rhythm was present. The remainder of the examination was not significant.

The day after admission the temperature reached 99.8 F., after which it returned to normal and remained so for the duration of hospitalization. The patient was digitalized for auricular fibrillation and minimal cardiac failure. Penicillin procaine, 600,000 units intramuscularly daily, and oxytetracycline, 500 mg. orally every six hours, were instituted on admission. Both drugs were discontinued on the third day because of a suspect drug reaction, following the appearance of swelling of both lips and the left cheek. The rales in the left lung base persisted, gradually decreasing in quantity, to Oct. 2, when no further abnormal sounds were heard on auscultation of the chest.

Chest x-ray taken the day of admission showed cardiomegaly, with pulmonary congestion and left lower lobe consolidation probably representing a pneumonitis. When x-ray was repeated on Oct. 1, the previously reported left basal consolidation had cleared; the cardiac enlargement was unchanged.

The blood sedimentation rate on Sept. 22 was 30 mm. in an hour (Wintrobe), and on Oct. 1 it was 28 mm. in an hour (Wintrobe). Urinalysis on Sept. 23 showed albuminuria. The blood Kahn reaction was negative.

No cold agglutinins were detected in repeated examination. The absorbed heterophile agglutination titer, done on Sept. 28, was negative.

Psittacosis-lymphogranuloma venereum group complement-fixation tests, performed on Sept. 22 and Sept. 29, were both positive in 1 : 64 dilution.

The patient was a retired policeman who raised parakeets as a hobby; he denied possessing any sick birds.

DIAGNOSIS

The clinical picture of psittacosis is supposedly uniform. Meyer † describes it as sudden in onset, with chilly sensations, fever, anorexia, sore throat, malaise, photophobia, and severe headache, or its beginning may be gradual and insidious. Fever was the only constant manifestation in the cases herein reported. The other symptoms are listed in order of incidence.

Fever	7
Cough	5
Pleuritic pain	4
Generalized aching and muscle pain	3
Anorexia	2
Chills	2
Dyspnea	2
Headache	2

TABLE 1.—*Significant Laboratory Findings in Seven Cases of Psittacosis*

Case	Leucocyte Count	Chest X-Ray	Serum Complement Fixation Titer
1.	8,250	Positive	1:20
2.	7,300	Positive	1:32
3.	6,800 8,400	Negative	1:256
4.	Not done	Positive	1:20
5.	9,600 8,800 8,050	Positive	1:128
6.	6,700 7,600	Positive	1:256
7.	10,100 10,500	Positive	1:64

TABLE 2.—*Results of Antibiotic Therapy of Seven Cases of Psittacosis*

Case	Drug *	Amount	Highest Temperature, F.	Duration of Fever	Response
1a.†	P	300,000 U IM daily	102	1 wk.	Poor
b.†	P	300,000 U IM daily	103	3 days	Poor
	C	500 mg. q. 4 h.	103.6	1 day	Good
2.	P	300,000 U IM daily	99.4	1 day	Good
3.	P	400,000 U IM daily	...	.....	.....
	and		105	2 days	Good
	C	500 mg. b. i. d.	...	.....	.....
4.	C	500 mg. q. 6 h.	102.8	2 days	Good
5.	O	250 mg. q. 6 h.	101	5 days	Fair
6.	O	250 mg. q. 6 h.	103	3 days	Good
7.	P	600,000 U IM daily	...	.....	.....
	and		100.8	1 day	Good
	O	500 mg. q. 6 h.	...	.....	.....

* P, penicillin; C, chlortetracycline (Aureomycin); O, oxytetracycline (Terramycin).
† a, first illness; b, second illness.

† Cited in Rivers.[1]

The laboratory findings in psittacosis are more constant (Table 1). The leucocyte count is normal or relatively low. Chest x-ray, though not characteristic, reveals areas of consolidation. The complement-fixation test may be negative at the onset, but it may become positive, with an increase in antibody titer, after the first week of illness. Chemotherapy may delay the appearance of antibodies for three to six weeks, and hence additional serum specimens must be examined.

The response to therapy in the cases presented has been uniformly good (Table 2).

COMMENT

Four of the seven cases presented were proved to be psittacosis by the demonstration of a fourfold rise in titer of complement-fixing antibodies against the psittacosis-lymphogranuloma group. Three of the cases were presumptive, because no rise in antibody titer could be demonstrated, although the titers varied from 1 : 20 to 1 : 256. A positive laboratory diagnosis of psittacosis depends on either isolation of the virus from the patient or the demonstration of a significant rise (fourfold) in complement-fixing antibody titer for the psittacosis-lymphogranuloma group. In only three of the cases was the diagnosis suspected clinically; in the remainder the diagnosis of psittacosis was made only after routine complement-fixation studies were reported positive for the psittacosis-lymphogranuloma group. This occurred despite the obvious clues of occupation or history of close contact with psittacine birds.

Most frequently these cases are considered to be primary atypical pneumonia. This is a likely diagnosis, since the symptoms and signs of psittacosis are clinically indistinguishable from those of primary atypical pneumonia. Smadel [2] found that 10 of 45 cases of primary atypical pneumonia selected at random were caused by strains of the virus of psittacosis; five additional patients in his series may have had psittacosis, but the diagnosis was indefinite because of the failure to demonstrate a significant rise in antibody titer in the convalescent sera of these patients. Bedson,[3] using only the demonstration of antibody by means of the psittacosis complement-fixation test, showed that 9 of 120 cases of primary atypical pneumonia were actually due to psittacosis. Eaton [4] found that 10% of a series of cases of primary atypical pneumonia were psittacotic in origin. In contrast, Jordan and co-workers [5] found antibodies for the viruses of the psittacosis group in only 2 of 67 cases of primary atypical pneumonia. This great variation in incidence of psittacosis among cases of pneumonitis may be due to the lack of repeated examinations of sera from suspected cases and possible interference with antibody formation due to antibiotic therapy. Meyer and Eddie state that examination of repeated serum specimens for complement-fixing antibodies with a twofold to fourfold increase in titer plus evidence of pulmonary involvement are sufficient evidence to warrant a diagnosis of psittacosis.[6] He also states that "a serum titer of 1 : 16 when obtained from a patient with clinical manifestations suggestive of psittacosis may be considered positive." [6]

The reported incidence of psittacosis is extremely variable. The incidence of the disease in Illinois is shown in Table 3. In Massachusetts 15 cases of psittacosis were reported in the four-month period from December, 1929, to March, 1930. Thereafter, three cases were reported from 1932 to 1946.[9] The nationwide distribution of the disease from 1942 to 1951, inclusive, showed the average annual number

of cases of psittacosis to be 23. The actual number varied from 1 case in 1943 to 35 cases in 1949. In 1952, reports on the occurrence of psittacosis were received from 12 of the 48 states; 70 cases were reported.[10]

The ubiquitous nature of psittacosis is best evidenced by reports of its occurrence in almost every portion of the world. It has also been recently reported in Australia and Israel.‡ Originally it was believed that the disease was transmitted to man only through contact with psittacine birds (Psittaciformes), including the parakeet, the cockatoo, the cockateel, the kea, the lorikeet, the lory, the lovebird, and the macaw, as well as the parrot. This assumption is incorrect, since there exists a psittacosis-like infection in the following species of birds: pigeons,§ chickens,‖ turkeys,¶ domestic ducks,[20] wild pigeons,[21] finches,[22] and sea gulls.[23] The occurrence of this disease among nonpsittacine birds is referred to as ornithosis. In view of the widespread dissemination of the psittacosis virus geographically and its presence in such a vast avian reservoir of both domestic and wild birds, the incidence of psittacosis previously quoted is probably incorrect.

TABLE 3.—*Incidence of Psittacosis in Illinois* *

Year †	Cases, No.
1945	2
1946	0
1947	0
1948	0
1949	1
1950	0
1951	4
1952	9
1953	34

* References 7 and 8.
† The figures from 1946 through 1953 represent the cases reported in the first nine months of each year only.

Other viral agents, similar to the virus of psittacosis, have been isolated from human sufferers with illnesses clinically similar to psittacosis. These diseases have a much higher mortality rate than has psittacosis.

Zichis and Shaughnessy [24] reported two fatal cases of an illness characterized by a gradual onset of weakness, malaise, fever, and head and chest pains and eventual pneumonic consolidation. At postmortem examination a virus was isolated which resembled that of psittacosis in many characteristics but was immunologically distinct from other members of the psittacosis-lymphogranuloma venereum group. This strain has been referred to as the Illinois virus.

A series of reports # dealing with a fulminant type of pneumonitis were published in 1944. This epidemic afflicted 19 persons, with 8 deaths. It was spread by direct contact from human to human, probably by the respiratory route. The causative agent was named the Louisiana pneumonitis virus. The illness was characterized by a mild onset with headache, malaise, backache, and chilly sensations.

‡ References 11 and 12.
§ References 13-15.
‖ References 16 and 17.
¶ References 18 and 19.
# References 25-28.

The incubation period was from 6 to 19 days. Pneumonitis developed on the third day. This virus produced pathologic changes in inoculated animals similar to those produced by the psittacine group of viruses.

The relationship of these viruses and the viruses of meningopneumonitis, human pneumonitis (S-F strain), mouse pneumonitis, feline pneumonitis, inclusion blenorrhea, and trachoma to the viruses of psittacosis and ornithosis has been thoroughly discussed by Cox [30] as well as by Meyer.* Mere mention of their occurrence is sufficient for our purposes.

The problem of control of psittacosis is a most pressing one. This would be a relatively simple measure if only birds of the psittacine group were instrumental in the transmission of the disease. Since we are now cognizant of a significant reservoir of the disease among domestic fowl as well, control measures are more difficult to initiate. Mandel and Jordan [16] believe that psittacosis is rarely a hazard for men handling chickens. They based their opinion on the results of an investigation of a case of possible ornithosis in a poultry store worker. The sera of 29 local poultry store workers were examined; six showed elevated titers for the psittacosis-lymphogranuloma group. Five of the six positives were obtained from Negro workers. Eighteen of 19 white employees had no serological evidence of infection. The authors believe that the antibodies in the sera of the Negro workers were not indicative of psittacosis but were probably due to past infection with the virus of lymphogranuloma venereum, which is antigenically indistinguishable from that of psittacosis. They based this assumption on the higher rate of lymphogranuloma and other venereal disease among Negroes. Irons and co-workers [19] described an explosive outbreak of psittacosis among turkey killers and dressers. This epidemic resulted in 22 cases, with 3 deaths in the group. This report is certainly at variance with the conclusions of Mandel and Jordan that psittacosis is not a great hazard among poultry workers.

Meyer states, in discussion after presentation of a paper by himself and Eddie,[29]

> I don't want to create now a good deal of fear that you shouldn't eat any ducks. You probably have done it a great many times and have never contracted psittacosis, but it is worthwhile to keep in mind that this new reservoir of psittacosis is enormous.

Perhaps Meyer implies that the hazards involved in contacting psittacosis by exposure to infected fowl are in the nature of a calculated risk, which should be assumed because the possibility of incurring the disease is minimal and the necessity of using the birds is great. This is very logical and correct. However, it cannot be applied to contacts with birds of the psittacine group or to pigeons, which serve no useful purpose and in many instances repay their protectors with illness and sometimes with death.

The need for more rigorous control of psittacosis has been the subject of various reports. A recent editorial in the *British Medical Journal* [31] called attention to a fatal case of psittacosis occurring shortly after the lifting of the ban on the importation of parrots.

A similar outbreak of psittacosis, the first in 10 years, occurred in Peekskill and in Ossining, New York, shortly after revocation of a law prohibiting the sale, breeding, or importation of psittacine birds into New York State and New York City, early in 1952. These cases were reported by Drachman,[32] who stated that

* Cited in Rivers.[1]

the New York State Department of Health had justified the repeal for the following reasons: (1) the diminishing public health importance of psittacosis, (2) the availability of effective therapeutic drugs, (3) the discovery of widespread reservoirs of psittacosis in nonpsittacine birds, (4) the negligible evidence that psittacine birds are more of a hazard in terms of transmission of the disease or harbor a more virulent virus strain, (5) the practical difficulties or impossibilities of adequately enforcing interstate quarantine regulations.

The fallacies in the above considerations are too obvious to enlarge upon. Fortunately, some states do not consider control of psittacosis as hopeless a matter as does New York.

Several months after New York State repealed its law, Illinois revised its regulations [33] to provide that "All persons dealing in psittacine birds shall keep a record of each transaction for at least two years. These shall be available for official inspection at all times." These regulations were passed when 10 cases of psittacosis were reported in two years, compared with a single case in the preceding four years.

We feel that the control measures against psittacosis suggested by a committee of the American Public Health Association [34] should be adopted and enforced on a national basis.

Another approach to prevention of psittacosis has been attempted. Quan and co-workers [35] tried to eradicate the virus from the tissues of infected parakeets by treating a series of birds with penicillin. The effort was unsuccessful, since the virus carrier rate in the treated groups was statistically undifferentiated from that in an untreated control group of birds 25 to 29 days after treatment was concluded.

Although eradication of the disease by legislation is at present difficult and elimination of the carrier state in birds has been unsuccessful, perhaps vaccination of all persons coming in close contact with psittacine birds or with other potential carriers is feasible. Rivers and Schwentker [36] noted that monkeys that have recovered from psittacosis have an increased resistance to infection with the virus and possess neutralizing antibodies against psittacosis virus in their sera. Monkeys vaccinated intramuscularly with unattenuated psittacosis virus have an increased resistance to the active agent and possess neutralizing antibodies in their sera. They considered that the intramuscular introduction of active psittacosis virus in moderate amounts into human beings appears to be relatively harmless and repeated inoculations result in the appearance of neutralizing antibodies in the sera.

The production of immunity in mice against the viruses of the psittacosis group was successfully performed by Francis and co-workers.[37] They used the safer method of inactivation of the vaccine rather than using active virus. This inactivation was achieved by the use of ultraviolet irradiation.

The treatment of psittacosis has improved greatly since the advent of antibiotic therapy. Good results have been reported with the use of penicillin by Heilman and Herrell, in 1944,[38] and others.†

The greater antiviral activity of chlortetracycline (Aureomycin), chloramphenicol (Chloromycetin), and oxytetracycline (Terramycin) makes these drugs the medications of choice in the treatment of psittacosis. In a recent paper, Maclachlan and co-workers [42] concluded that the effect of antibiotics on the course of psittacosis was questionable but that they should be given; best results were obtained with

† References 39-41.

penicillin. Bassett [43] used oxytetracycline in the treatment of three cases of psittacosis, and she believed that the drug played a definite part in their improvement. In contrast to these reports, the most satisfactory clinical response in our series was obtained with chlortetracycline and oxytetracycline (Table 3).

The transmission of the disease from human to human is reported to be infrequent, although several instances of such transmission have been noted. Meyer and Eddie [44] reported a case of a human carrier of psittacosis virus, who harbored the virus for 8 to 10 years after a severe acute attack. Despite the long carrier state, he apparently did not transmit the disease to any contacts. Patients with active psittacosis shortly after recovery have spread the disease to other human beings (case of Vervoort and Ruys, cited by Meyer and Eddie [44]); patients have spread the disease to nurses, and there was an outbreak of pneumonitis in Louisiana, previously mentioned; these are all illustrations of the potentially infectious nature of the disease and the necessity for isolation of cases and contacts. Case 4 of the present series is an excellent example of the transmission of the disease by direct contact with a human case. The patient's illness began 17 days after initial contact with a known case of psittacosis and with no opportunity for contact with psittacine birds. It also demonstrates the inefficacy of penicillin and chlortetracycline as prophylactic measures against psittacosis, because this patient received both of the aforementioned drugs during the incubation period of the disease. Possibly the patient did not receive adequate amounts of either penicillin or chlortetracycline for prophylaxis. Despite its prophylactic failure, there was an excellent therapeutic response to chlortetracycline.

The question of immunity to psittacosis and whether it is conferred by a single attack of the disease should also be considered. It is generally believed that this is so. Cox discussed this problem [30] and cites Wenkebach's report of a proved reinfection with the disease. It is unfortunate that the serum in Case 1 was not tested during the first illness for complement-fixing antibodies against the psittacosis-lymphogranuloma venereum group. It may be assumed on clinical grounds that both illnesses were due to psittacosis, although the first episode may have been a primary atypical pneumonia of different etiology.

SUMMARY AND CONCLUSIONS

Four proved and three presumptive cases of psittacosis are presented. The diagnosis was established by the demonstration in the serum of complement-fixing antibodies in significant titer for the psittacosis-lymphogranuloma venereum group.

The clinical and laboratory data of the seven cases are discussed and evaluated. These cases varied in severity from a mild upper-respiratory-infection-like illness to a rather severe pneumonitis. There are no diagnostic clinical criteria for psittacosis.

The response to specific therapy is evaluated; chlortetracycline and oxytetracycline appear to be most effective.

The mounting incidence of psittacosis is discussed, and the need for more adequate control measures against the spread of the disease is emphasized.

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PREVALENCE OF MANIFEST ATHEROSCLEROSIS IN A WORKING POPULATION

Preliminary Report

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ACCURATE data on the prevalence of disease in the total population are rarely obtainable. No previous attempt appears to have been made to determine the prevalence of atherosclerosis in an unbiased sample of a population.* An opportunity for such a study presented itself when a labor union, the New York Joint Board of the Amalgamated Clothing Workers of America, provided a grant for medical research at their outpatient clinic, the Sidney Hillman Health Center. The present report is concerned with the over-all prevalence of atherosclerosis among members of this union. It is the eventual purpose of the study to discover possible relationships between atherosclerosis and factors such as ethnic origin, familial predisposition, dietary habits, body build, and serum lipid patterns. The data collected are, as yet, insufficient to give definitive answers to all of these questions, which will be the subject of future reports.

The union population is not, of course, representative of the population of the country as a whole. Most of the workers are of Italian or Jewish origin, having come to this country in their youth. The sample excludes persons who have changed their trade or retired from work on account of illness or other reasons. The sample is thus biased in favor of healthy people, unlike population samples consisting of patients in hospitals or clinics, so that our prevalence figures will be too conservative rather than too high. Patients with known coronary artery disease who have returned to work are included. Experience with a similar population group showed that approximately 80% of persons with clinical coronary artery disease continue to work.[2] Others have had similar experiences.[3] Patients who sustained cerebrovascular accidents, on the other hand, will not frequently appear in the sample, since their condition usually precludes full employment.

DESCRIPTION OF SAMPLE

The sample† is representative of a union population of 32,000 employed male and female garment workers, excluding those under 40 years of age.

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* The Framingham Heart Disease Epidemiology Study of the United States Public Health Service,[1] although not specifically directed towards this end, will yield valuable data in this connection.

† Dr. John W. Fertig, Professor of Biostatistics, School of Public Health, Columbia University, assisted us in the preparation of the sampling plan.

Proportional representation is given to the various trades in the Union (coatmakers, pantsmakers, cutters, etc.) and to shops of various sizes. The sampling is carried out in two stages. With the use of tables of random numbers, first, a sample of shops is drawn from a list of Union shops in New York City; second, a sample of workers is drawn from a list of workers in each of these shops. If, in the process of sampling, a person under age 40 happens to appear, his or her name is discarded. Names are collected until approximately one sixth of the workers in the shop are chosen. Of 630 workers drawn, 568 (i. e. 90%) have presented themselves for examination.

The present report is based on a sample of 343 men and 225 women, selected as described. The mean age of the men was 60 years; that of the women, 54 years. The age distribution is shown in Table 1. Thirty-six per cent of the men and 51% of the women were of Italian origin; 54% of the men and 28% of the women were of Jewish origin. The remaining 10% of the men and 21% of the women represented various ethnic groups, mostly natives of northeastern Europe; a few were Negroes.

TABLE 1.—*Age Distribution of Sample*

Age, Yr.	Cases, No.	
	Men	Women
40-49	65	75
50-59	133	98
60-69	127	52
70-79	18	..
All ages	343	225
Mean age	59.8	54.0

METHODS

Examinations are carried out at the Research Department, which is maintained as a separate unit of the Health Center, with its own staff and laboratory. Each examination includes the following: family and medical history, dietary history, complete physical examination, 12-lead electrocardiogram, posteroanterior chest roentgenograms and lateral roentgenograms of the abdomen for evidence of aortic calcifications, blood tests (glucose, cholesterol, phospholipid, uric acid, serological test for syphilis), and urine examination.

The diagnosis of atherosclerosis is made whenever evidence of coronary, peripheral, or cerebral artery disease or aortic calcifications, alone or in combination, are found.

The diagnosis of coronary disease is based on a definite history of angina pectoris [4] or myocardial infarction or on the following characteristic electrocardiographic signs: Q_1T_1 patterns, Q_3T_3 patterns with concomitant changes in Lead aV_F, abnormal Q waves (Q being 20% or more of QRS in Leads I and/or II, 30% or more of QRS in Leads V_5 and/or V_6, or 50% or more in Lead aV_F), widening of the QRS interval to 0.12 second or more in the absence of undue cardiac hypertrophy, or S-T elevations or depressions of 2 mm. or more in one or more leads, unaccounted for by left ventricular strain, digitalis, or transient causes.

Peripheral artery disease is diagnosed when two or more pulses in one leg or one or more pulses in each leg are absent in the femoral, popliteal, anterior, or posterior tibial arteries. No importance is attached to absent pulsations in the dorsalis pedis arteries. It is agreed that the absence of pulsations in the major arteries is the most reliable single sign of occlusive arterial disease in the legs.[5] It is occasionally difficult to be certain whether a given pulsation is present, diminished, or absent. In such cases, postural color changes and, despite their limited value, oscillometric readings have been used as additional guides. Symptoms of intermittent claudication, without objective signs of arterial insufficiency, are not considered diagnostic of peripheral artery disease, since true occlusive disease rarely if ever occurs unless there is absence or diminution of peripheral pulsations.[5]

Cerebral atherosclerosis is diagnosed from a history of a major stroke or an attack of sudden transient dizziness, aphasia, or mental confusion, accompanied by unilateral palsy, or signs of residual lesions of the central nervous system.

Aortic calcifications are diagnosed from posteroanterior 6-ft. (1.8-meter) chest plates and lateral views of the abdomen. The chest films are slightly overpenetrated in order to reveal calcifications more clearly; on an average, 66 kv., 300 ma., with an exposure of 1/10 second is used. Lateral roentgenograms of the abdomen are taken with a Bucky grid at a distance of 36 in. (90 cm.), using 100 ma., an exposure of 2 seconds, and an average of 85 kv., depending on

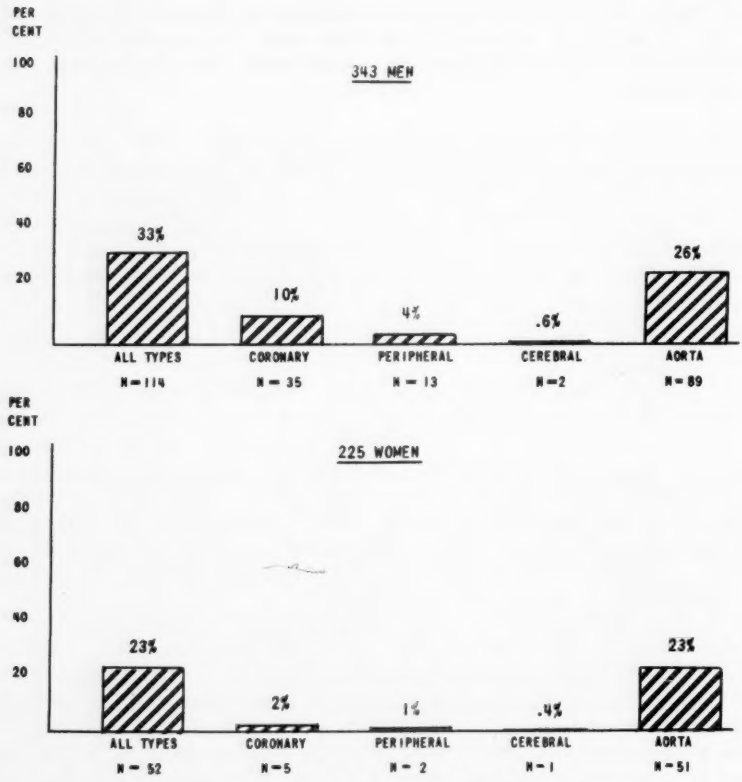

Chart 1.—Prevalence of atherosclerosis by site of lesion.

size of the patient. Calcification of the thoracic aorta is diagnosed if definite crescentric shadows are seen in the aortic knob. Calcification of the abdominal aorta is diagnosed in the presence of single linear densities at least 1 cm. long or multiple streaks, in line or parallel, in the proper location. Advanced calcification that outlines the aorta is easily recognized.‡

‡ A separate study, comparing premortem roentgenograms with autopsy findings, has given us assurance that our interpretations of these roentgen-ray shadows are correct. It has also shown that calcifications diagnosable by roentgen ray represent true intimal and usually advanced atheromata.[6]

FINDINGS

Thirty-three per cent of the men and 23% of the women had one or more of the selected stigmata of atherosclerosis (coronary, peripheral, or cerebral artery disease or aortic calcifications), as shown in Chart 1. The frequency of atherosclerosis increased steadily with age in both sexes. In their 60's, about half the men and women showed some manifestation of atherosclerosis.

Table 2 shows the prevalence of atherosclerosis by site of lesion. In the random sample to date, 10% of the men and 2% of the women had evidence of coronary disease; the corresponding figures for peripheral artery disease were 4% in men and 1% in women; those for cerebrovascular disease were 0.6% in men and 0.4% in women. As many as 26% of the men and 23% of the women evidenced aortic calcification on the roentgen film. In the men 19% of the calcifications were in the thoracic aorta, 62% were in the abdominal aorta, and 19% were in both sites; for women the corresponding figures are 14%, 67%, and 19%.

The distribution of atherosclerosis according to site of lesion in the 114 men and 52 women with manifest arterial disease is shown in Chart 2. The lower sec-

TABLE 2.—*Prevalence of Atherosclerosis by Site of Lesion*

	Men		Women	
	No.	%	No.	%
Total examined	343	100.0	225	100.0
Atherosclerosis, all sites	114	33.2	52	23.1
Coronary atherosclerosis *	35	10.2	5	2.2
Cerebral atherosclerosis *	2	0.6	1	0.4
Peripheral atherosclerosis *	13	3.8	2	0.9
Aortic atherosclerosis *	89	25.9	51	22.7

* With or without other manifestations of atherosclerosis.

tions of the bars indicate the percentage of persons who had a given lesion unassociated with other stigmata of atherosclerosis; the upper, cross-hatched, sections indicate combined lesions. The coronary arteries were involved in 35 men (31%) and 5 women (10%); the cerebral arteries, in 2 men (2%) and 1 woman (2%), and the peripheral arteries, in 13 men (11%) and in 2 women (4%). Of particular interest are the data on aortic calcifications. Eighty-nine men (78%) and 51 women (98%) showed evidence of calcification. In 71 men (62%) and 46 women (88%) this was the only clinical evidence of the disease.

The great number of cases in which calcification of the aorta is the only recognizable sign of atherosclerosis is striking. If these were eliminated, the prevalence of atherosclerosis in this series would be 14% instead of 33% for men and 3% instead of 23% for women. In sharp contrast to coronary sclerosis, aortic atherosclerosis occurs as frequently in women as in men and accounts for the unusually high prevalence of atherosclerosis in women. This high incidence of aortic atheromatosis in both men and women has been well known to pathologists for over 100 years.§ Clinicians have paid little attention to it, apparently because the lesion rarely gives rise to disorders of function.

Hypertension and diabetes are known to be associated with atherosclerosis and possibly to favor its development. It has been suggested that obesity plays a

§ References 7-10.

similar role.[11] It is important, therefore, to determine to what extent the frequency of these three conditions affects the prevalence figures of atherosclerosis in this sample. As yet, we do not have a sufficient number of cases to permit a detailed analysis of these relationships.

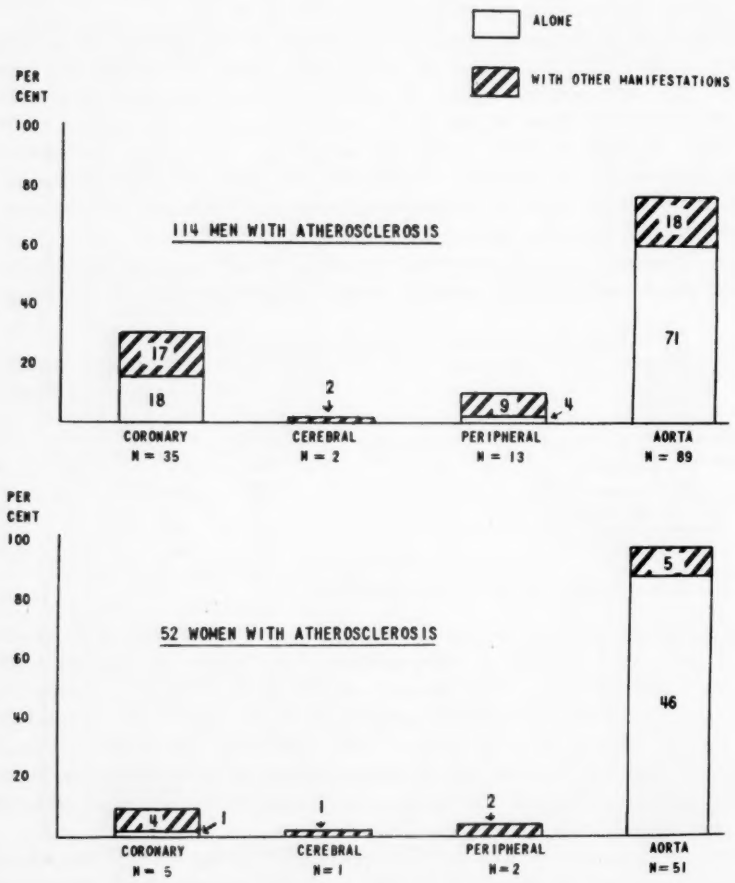

Chart 2.—Distribution of atherosclerosis by site of lesion.

Twenty-five per cent of the men and 37% of the women had hypertension.‖ Atherosclerosis appeared to be commoner in the hypertensives in both sexes. However, in approximately half of the cases with aortic calcifications this condition was unassociated with hypertension.

‖ Two blood pressure readings were taken in the recumbent position, at a 20-minute interval. Two systolic readings over 150 mm. Hg or one diastolic reading over 95 mm. Hg were taken as indicative of hypertension.

Five per cent of the men and 8% of the women in the sample had diabetes. Forty-seven per cent of the 17 men and 50% of the 18 women with diabetes had evidence of atherosclerosis.

Forty-one per cent of the men and 54% of the women were 10% or more above standard weight, calculated from the medicoactuarial tables.[12] Although the sample is clearly weighted with obese persons, analysis of the data did not support the contention that there is an association between obesity and atherosclerosis. Thirty-four per cent of the obese men and 22% of the obese women manifested atherosclerosis, as compared with 33% of the men and 25% of the women of approximately standard weight. Garn and associates[13] and Ungerleider and Gubner[14] likewise found no association between atherosclerosis and obesity.

COMMENT

Our study has highlighted the great frequency of diagnosable atherosclerosis of the aorta, as well as its equal prevalence in men and women over age 40. Manifest coronary artery disease is far less common and, in accord with other studies, occurs far more frequently in men. Sixteen per cent of men, but only 8% of women, with

TABLE 3.—*Serum Cholesterol*

	Serum Cholesterol, Mg./100 Cc.			
	Men		Women	
Age, Yr.	Mean	N	Mean	N
40-49	231	65	251	74
50-59	240	132	259	96
60-69	230	127	263	52
70-79	214	18	...	..
All ages	234	342	257	222

aortic atherosclerosis had manifest coronary sclerosis as well. The unknown forces that cause this selective localization of atherosclerosis would appear to be etiologic factors just as important as the disturbance of lipid metabolism, which is currently regarded as the chief cause predisposing to atherosclerosis.

Many authors have established serum lipid patterns characteristic of persons with atherosclerosis by comparing serum lipids of persons with atherosclerosis with the serum lipids of those presumably free from the disease. These investigations have established a relationship, not necessarily causal, between certain lipid patterns and manifest coronary atherosclerosis. In such studies, the coronary arteries have been singled out as indicators of atherosclerosis. It is evident that among the "normal" control group there are many with aortic atheroma. Even if these were eliminated there would remain many with subclinical atherosclerosis. A determination of the number of persons in a given population who exhibit a metabolic error that may lead to atherosclerosis should include in the atherosclerotic group all subjects who show any and every evidence of atherosclerosis. Even this would overlook many with latent atherosclerosis.

Conclusions drawn from patients selected by virtue of the presence of coronary atherosclerosis alone may be misleading, for involvement of the coronary arteries may depend on factors other than the metabolic error. Possibly the low incidence of coronary atherosclerosis in women is due, not to a more perfect lipid metabolism,

but to some local factor that spares the coronary arteries but not the aorta. Although at younger ages women have lower levels of certain lipids than men,¶ the converse appears to be the case in the older age groups. Our own serum cholesterol figures # (Table 3) conform with the trends previously reported for older men [18] and women.* Possibly it takes a higher concentration of cholesterol in the serum, or a higher cholesterol-phospholipid ratio,† to induce disease in the coronary arteries than is required in the aorta.

Katz and Stamler [21] have shown that estrogen administered to cholesterol-fed cockerels inhibits coronary atherosclerosis but is without effect on the development of aortic atheroma. Katz emphasizes that in chickens different laws determine atherogenesis in the aorta and in the coronary arteries, and he suggests that similar conditions may obtain in humans. Our data support this contention.

SUMMARY

Data are presented on the prevalence of manifest coronary, peripheral, cerebral, and aortic atherosclerosis; hypertension; diabetes, and overweight in a random sample of working men and women age 40 and over. The over-all prevalence of atherosclerosis was 33% in men and 23% in women. In contrast to coronary disease, manifest aortic atherosclerosis is as frequent in women as in men. The importance of aortic calcification as a recognizable stigma of atherosclerosis is discussed.

Mrs. Rita Simpson coordinated the study and coded and prepared the data for analysis. Dr. Julian B. Hyman helped with the examinations. Mr. M. Wurm has been responsible for the chemical analyses.

¶ References 15 and 16.

Cholesterol determinations were performed by the method of Abell and co-workers.[17]

* References 19 and 20.

† References 21 and 22.

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INFILTRATIVE EOSINOPHILIA

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INFILTRATIVE eosinophilia is a condition characterized by a marked relative and absolute increase in the circulating mature eosinophiles and an inflammatory reaction with a profuse infiltration of this cell. It has been reported in the literature under these various names: Loeffler's syndrome,* tropical eosinophilia,† acute febrile eosinophilic asthma,[21] pulmonary eosinophilia,[21] pulmonary eosinophiliosis,‡ eosinophilic infiltration of the lungs,§ eosinophilic asthma,[40] Weingarten's syndrome,[17] pseudotuberculosis of the lungs,|| benign eosinophilic leukemia,¶ familial eosinophilia,# pulmonary acariasis,* lecithinophil eosinophilia,† *grande eosinophilié sanguinaire*,[68] eosinophile lung,‡ eosinophilia with splenomegaly,§ eosinophilic pneumopathy,|| and pulmonary infiltration with eosinophilia (P. I. E.).[61]

Since all the reported cases present many traits in common, differing only in the degree of severity of the symptoms and their duration, it seems convenient to group them under the term infiltrative eosinophilia. Although Loeffler's syndrome implies a short clinical course with transitory roentgenological pulmonary alterations, some of Loeffler's cases showed a tendency to chronicity, and several observers claim that such cases are instances of "tropical eosinophilia." However, Loeffler's syndrome occurs in both the temperate and tropical zones, it is at times accompanied by asthma, and it is considered a systemic rather than an exclusively pulmonary disease.

It must be emphasized that generally the clinical picture is dominated by symptoms simulating bronchial asthma in the subacute or chronic stages. However, in

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* References 1-5.

† References 6-20.

‡ References 22 and 23.

§ References 24-39.

|| References 41-46.

¶ References 47 and 48.

References 49 and 50.

* References 74-76.

† Greval, S. D. S., cited by D'Abrera and Stork.[19]

‡ References 51-55.

§ References 56-58.

|| References 59 and 60.

some instances there is an acute onset, with chills, fever, generalized body aches and pains, nausea, vomiting, diarrhea, and generalized abdominal pain, before the appearance of pulmonary symptoms. In addition, the liver, spleen, lymph nodes, muscles, stomach,[95] epididymis, skin, and bone marrow, as well as the lungs, may show a marked eosinophilic infiltration, and there may be an increase in serum globulin and a hastened sedimentation rate. All of this tends to suggest a systemic disease whose dominant pathologic alteration is an infiltrative eosinophilia.

ETIOLOGY

Chronic infiltrative eosinophilia may be associated with parasitic infestations or with frequent intercurrent upper respiratory infections. There is a large group of cases with no obvious fundamental or precipitating cause. In the great majority the cause is elusive, but the overwhelming consensus supports hypersensitivity to various allergens as the underlying defect.

Some cases have been associated with infestations with Ascaris lumbricoides,¶ Schistosoma mansoni,# Filaria bancrofti,* Fasciola hepatica,[68] Endamoeba histolytica,[69] Necator americanus,[70] Strongyloides stercoralis,[71] Trichinella spiralis,[72] Clonorchis sinensis,[73] the Acarus mite,† and Toxocara canis (larva migrans).‡

There is no definite experimental proof either to support or deny the causative role of parasitic infestation in this condition. The reaction of the host has not been adequately studied. The nature of the parasite, the magnitude of the infestation, the physical condition of the host, and the reaction of the tissues appear as the most important governing factors. Why some patients should respond with a massive eosinophilia to parasitic infestation while others do not is a subject for speculation.

The common denominator appears to be close contact of the larvae, mature parasite, or ova with the host's tissues. This is exemplified by the marked eosinophilia observed during the larval migration in heavy infestations with Ascaris lumbricoides § and Necator americanus [70] and the similar response during the period of maturation and oviposition in Manson's schistosomiasis. The failure of specific therapy (anthelmintics) to correct the eosinophilia is no valid argument against a parasitic cause, since, in special instances, it appears as if the eosinophilia may be perpetuated by the response of the tissues to products of dead, disintegrating parasites or their ova.

The close association of infiltrative eosinophilia with upper respiratory infection is at times evident, although bacterial specificity remains undiscovered. Transient pulmonary infiltrations, with asthma and purpuric manifestations of the skin, have been produced by the injection of vaccines autogenous to man.|| The high cold hemagglutinin titers, the acute onset, and the roentgenologic similarity of this condition to viral pneumonia have led some observers to suggest a viral etiology.¶ However, this has had no experimental support because of the lack of adequate

¶ References 63-65.
# Díaz-Rivera, H. S., and Ramos-Morales, F.: Unpublished data.
* References 66 and 67.
† References 74-76.
‡ References 77 and 78.
§ References 63-65.
|| References 82 and 83.
¶ References 19, 22, and 23.

studies. The effectiveness of arsenical compounds and the doubtful serologic tests for syphilis led some Hindu workers to suggest a spirochetal etiology or an arsenic-sensitive organism as the causative agent.[19] The failure to isolate spirochetes from the sputum, the ineffectiveness of penicillin, and the negative serological tests for syphilis in the great majority of cases reported do not lend support to this idea. There is no definite relationship between pulmonary tuberculosis and infiltrative eosinophilia, although both conditions may occur together. Coccidioidomycosis [79] and allergy to convallaria and privet plant pollens # and to penicillin oil and beeswax [81] are other possible pathogenetic factors.

Breton [1] reports an incidence of 6 to 8% of infiltrative eosinophilia accompanying bronchial asthma. A long-standing bronchial asthma may occasionally precede the appearance of infiltrative eosinophilia.* However, the relation between the two conditions is not clear, since infiltrative eosinophilia appears to be pathogenetically different from bronchial asthma. Although the exact incidence is unknown, allergic rhinitis is claimed as a frequent precursor and accompaniment of the condition. Skin manifestations, infrequently reported, appearing in the early phase of the disease, warrant further studies. Some cases of severe periarteritis nodosa with eosinophilia, asthma, and transitory infiltrations are indistinguishable from infiltrative eosinophilia. This close association has been infrequently stressed,† but it can be speculated that, in many instances, infiltrative eosinophilia and periarteritis nodosa may be gradations of a common underlying allergic process.

PATHOLOGY

Our knowledge of the pathologic changes in this condition is limited by the small number of autopsies reported in the literature.‡ Grossly, the lung presents consolidation in the form of multiple grayish-yellow firm nodules, 5 mm. or more in diameter, which are widely distributed. There is thickening of the wall of the bronchi, and exudate is found in their lumina. Microscopically, there is marked eosinophilic infiltration ("eosinophilic pneumonia"), at times accompanied by fibroblastic proliferation ("unresolved eosinophilic pneumonia"). There may also be tubercle-like lesions surrounded by a profusion of eosinophiles and with occasional atypical giant cells. The bronchial walls show edema and infiltration with eosinophiles, with marked exudation into the lumina. The muscle elements do not undergo hypertrophy. The lesions encountered in the blood vessels are indistinguishable from those of periarteritis nodosa. The liver presents multiple small firm yellowish-gray nodules, which microscopically show a central area of necrosis and a dense infiltration with eosinophiles. Occasionally, parasites or their ova are encountered in liver sections. However, the above-described lesions may be remote from the parasite or ova. Healing, with disappearance of the eosinophilia, leads to fibrosis.

It must be emphasized that the alterations in the bronchial wall are indistinguishable from those of bronchial asthma, except for the absence of muscular hypertrophy. The more advanced pathologic changes in the lungs and liver are typically granulomatous.

References 26 and 80.
* References 1, 82, and 83.
† References 82-84 and 94.
‡ References 2, 23, 31, 36, and 62.

It appears as if the initial pathologic alteration is exudative. The earliest pulmonary changes can be compared to the allergic pneumonia of rabbits,[87] with edema of the bronchial epithelium and swelling of the alveolar lining. This may be accounted for by increased capillary permeability. Edema of the basement membrane and submucosa may follow, with increased exudation. Profuse infiltration of the pulmonary parenchyma with eosinophiles leads to the clinical and roentgenologic picture of bronchopneumonia. The asthmatic manifestations result from changes in the bronchial walls and accumulation of exudate in their lumina. Edema, and often necrosis, of the walls of blood vessels may accompany this reaction.[2] The appearance and disappearance of lesions in this exudative phase explains the transitory roentgenologic manifestations. The final trend is toward organization of the pulmonary and hepatic lesions.

CLINICAL PICTURE

The onset may be either insidious or acute, but once established the disease follows an invariable course, with a tendency to chronicity. In some, the acute onset is ushered in by body aches, high fever (temperature to 103 F.), gastrointestinal symptoms (nausea, vomiting, diarrhea), paroxysmal cough with scanty sputum, and tightness and wheezing of the chest. In others, the onset is characterized by a violent attack of asthma, which may require heroic emergency measures. Physical examination reveals acutely ill patients in variable degrees of respiratory distress, from the mildest to the severest. The liver, spleen, and lymph nodes may be enlarged.

The insidious onset is characterized by lassitude, weakness, general malaise, moderate dyspnea, loss of weight, paroxysmal cough with scanty sticky sputum, and wheezing.§ The respiratory symptoms are worse during the late afternoon and evening hours, gradually subsiding during the late hours of the night or early morning.

The persistence of the symptoms may force the patient to seek medical attention months or years after the onset. Results of the physical examination may be completely normal, aside from moderate to severe pulmonary emphysema, malnutrition, occasional wheezes, and scattered rales, especially when the patient is examined in the morning. The lymph nodes, liver, and spleen may be enlarged.

In another group of patients the onset cannot be accurately determined, the discovery of the condition being purely accidental. However, a history of mild attacks of bronchial asthma may be elicited in some of these patients.

The course and duration of the illness is variable. In some instances with an acute onset, severe symptoms may last no more than one or two weeks, with gradual, unaltered subsidence.|| In others, frequent exacerbations follow, running a variable course of more than three months' duration. Exacerbations of pulmonary symptoms appear at varying intervals of weeks or months. In some, the exacerbations are precipitated by upper respiratory infections; in others, precipitating factors are lacking. Severe status asthmaticus may appear. However, the pulmonary symptoms are usually mild or moderate in intensity and the patient is able to perform light

§ References 6, 21, 23-25, and 41.

|| References 22-25.

work. Pregnancy does not appear to ameliorate the attacks of asthma. In those in whom the main pathologic alterations reside in the liver the pulmonary symptoms are either mild or absent.

LABORATORY FINDINGS

An increase in the circulating eosinophiles, varying from 2,000 to over 100,000 per cubic millimeter of blood, is the most remarkable feature. The eosinophiles are mature, and only in rare instances are juvenile forms seen. The inconstant finding of an increase in the lobulations of the nuclei has been claimed as pathognomonic of the disease.[44] The actual number of circulating neutrophiles, lymphocytes, and monocytes remains unaffected. In a study of over 1,000 smears in 25 cases of our own, we failed to encounter either juvenile eosinophiles or inclusion bodies.¶ The hemoglobin and red cell values show a tendency to slight diminution but are otherwise unaffected. The bone marrow is overpopulated with eosinophilic elements, which sometimes comprise 60% of the cellular components. These consist mainly of mature eosinophiles, eosinophilic metamyelocytes, and, to a less extent, eosinophilic myelocytes. The sedimentation rate is generally accelerated. The serum globulins are usually increased, with elevation of the gamma fraction.[62]

The sputum is scanty, sticky, stringy, and whitish or yellow. Microscopic studies show many eosinophiles, most of them mature, although large mononuclear cells are not infrequently seen. No organisms have been consistently cultured nor have spirochetes been observed on dark-field examination. The Acarus mite has been recovered from the sputum of some patients, but only a few cases of infestation with this parasite exhibit eosinophilia.# The high incidence of positive or doubtful serologic reactions for syphilis stressed by some workers has not been observed by others.[21] The agglutination reactions with Proteus OX19 and OXK are consistently negative.[19]

The roentgenologic appearance of the lungs is variable. The lungs may be normal or there may be alterations indicative of chronic bronchitis or bronchial asthma in a minority of the cases. The dominant picture is that of a heavy infiltration of the pulmonary parenchyma, either transitory or permanent, depending on the duration of the disease. The transitory infiltrations may last for 3 to 12 days, at times disappearing without treatment. The size of the individual lesions may vary from very small, barely detectable to the naked eye, to a consolidation of a whole lobe. The lesions may be found in any location in both pulmonary fields and may appear as fluffy, irregular, soft infiltrates with hazy borders. At times they are migratory, disappearing in one area to appear in others. This variation in the roentgenologic picture may occur from one day to another.

Although the chronic alterations are generally represented by diffuse parenchymatous lesions of variable size, the miliary form predominates and presents a fairly typical roentgenologic picture. When films are observed from a reasonable distance, the architecture of the periphery of the lung is seen to be altered by fine reticular shadows, at times presenting a honeycombed appearance. Close inspection demonstrates numerous small nodules, varying in diameter from 1 to 5 mm. and distributed in an irregular manner throughout both lungs. The picture simulates a spider web sprayed with multiple droplets of white paint.

¶ Díaz-Rivera, R. S., and Ramos-Morales, F.: Unpublished data.

References 74-76.

With healing, either spontaneously or after therapy, roentgenologic evidence of cicatrization remains. The nodules appear smaller, and fine reticular shadows radiate from their surfaces, producing a stellate effect. Small linear scars, which may disappear as the years elapse or after the development of pulmonary emphysema or fibrosis, may be the only remnants of a previously active process.

Although chronic and transitory lesions may at times be seen in one patient, the dominant roentgenologic picture generally depends on the duration of the condition. The extent of parenchymatous involvement, as shown roentgenologically, seldom bears any relationship to the severity of the clinical manifestations. It must be emphasized that severe asthmatic bronchitis may occur in the absence of pulmonary infiltrations, while pulmonary symptoms may be relatively mild in cases with extensive parenchymatous involvement. In general, it appears that the liver is most heavily infiltrated with eosinophiles when the pulmonary parenchyma appears normal.

TREATMENT

Some forms of infiltrative eosinophilia respond efficiently to specific therapy, as exemplified by instances of heavy infestations with intestinal parasites. In some cases the eosinophilic count may decrease spontaneously together with disappearance of the pulmonary manifestations, not to reappear until reinfestation occurs. In others, the pulmonary manifestations may appear before onset of eosinophilic leucocytosis. In early stages of human schistosomiasis prior to oviposition the pulmonary infiltrates are probably the result of the passage of the larvae through the lungs. Most of these forms of infiltrative eosinophilia are not amenable to therapy with any of the arsenical preparations. Furthermore, many cases of infiltrative eosinophilia without evident cause, but accompanied by infestation with intestinal parasites, fail to respond to the anthelmintics. It can be speculated that in these instances the patient received inadequate anthelmintic therapy or that the dead parasites or their ova perpetuated the eosinophilia. Also, reinfestation may have occurred or the parasite may not be responsible for the disease. Our observations * in acute cases of Manson's schistosomiasis and in massive infestation with A. lubricoides and N. americanus show that the eosinophilia encountered in these diseases is unaffected by the administration of arsenic, which, of course, is not lethal to those parasites.

The newer antibiotics and chemotherapeutic agents are ineffective. Aminophylline and other bronchodilators are only of transitory symptomatic benefit. Intravenous typhoid vaccine produces a marked but transitory decrease in the number of circulating eosinophiles; yet no lasting remission is attained.† Favorable results with the use of corticotropin (ACTH) have appeared in the literature, but this needs further exploration (see Report of a Case).

In some instances, arsenic by mouth or by vein is the treatment of choice. Oxophenarsine hydrochloride (Mapharside) and neoarsphenamine are equally effective. Carbarsone and potassium arsenite (Fowler's solution) are as effective as the intravenously administered arsenicals. The minimum curative dose of arsenic is not known. Generally, four to eight intravenous injections of 0.04 gm. of oxophenarsine hydrochloride given at five-day intervals are curative. One of our patients who has been observed for three years received two injections of 0.04 gm. of oxophenarsine

* Díaz-Rivera, R. S., and Ramos-Morales, F.: Unpublished data.

† Díaz-Rivera, R. S., and Ramos-Morales, F.: Unpublished data.

hydrochloride, with rapid disappearance of symptoms but with persistence of the eosinophilia. It must be emphasized that after the initiation of treatment a period of two to four months may elapse before the eosinophile count returns to normal and that the eosinophilic infiltration of the viscera varies in direct proportion to the circulating eosinophiles. The persistence of symptoms of asthma after a return of the hemogram to normal indicates the coexistence of spasmodic bronchial asthma, which at this juncture may be relieved by aminophylline and other bronchodilators. A second course of arsenicals is indicated in case of relapse, provided the clinical picture is accompanied by eosinophilia.[23]

PROGNOSIS

Progress reports on large series of cases are lacking. Although Bass [58] reports on a patient who recovered spontaneously after a 12-year illness, relapses and exacerbations are the rule, and durable spontaneous remissions are rare. The degree of residual emphysema depends on the duration and severity of the pulmonary symptoms. A certain degree of liver damage probably persists after recovery.

REPORT OF A CASE

R. de L., a 32-year-old white Puerto Rican housewife, was admitted to the San Juan Hospital, stating that since 1941 she had suffered from frequent "nasal colds" with watery discharge and from severe sneezing at irregular intervals throughout the year, persisting for approximately seven days. These episodes were aggravated and, at times, precipitated by inhalation of house dust. On Feb. 1, 1950, while pregnant, she experienced a sensation of tightness of the chest, mild wheezing, and dyspnea on exertion; wheezes and rales were detected over both lungs posteriorly. During the months of March, April, and May, the wheezing and tightness of the chest increased in severity and were accompanied by paroxysmal cough in the afternoon and evening. Prior to a normal, full-term, spontaneous delivery, on May 23, 1950, she developed mild edema of the ankles, without hypertension. At that time the examination of the chest was within normal limits; the red cell count was 2,810,000, with 60% hemoglobin, and white cell count was 12,350 per cubic millimeter with 26% eosinophiles. The stools showed ova of Trichuris trichiura. Urinalysis and blood serologic tests for syphilis were negative. On May 25, 1950, a Pomeroy sterilization was performed, with an uneventful postoperative course. On May 27 the white cell count was 15,300 per cubic millimeter, with 18% eosinophiles.

The watery nasal discharge, sneezing, tightness of the chest, and cough continued through June, 1950, and at this time hoarseness and fever appeared. The fever was intermittent, preceded by chilliness, appearing during the evening, subsiding during the night, and persisting for two weeks. With the onset of the fever, the sneezing and nasal discharge were ameliorated, but the hoarseness persisted for a week. The cough was paroxysmal; it was productive of very scanty viscid yellowish sputum, was accompanied by tightness of the chest, and persisted until admission. The patient claimed that she felt well in the morning but that about 4 p. m. she would develop a hacking paroxysmal cough, with dyspnea, tightness of the chest, and wheezing. The severity of the coughing spells "forced her out of bed to catch her breath," and she was more comfortable only when sleeping with two or three pillows. With the development of weakness, dizziness, and general malaise during August, the white blood cell count was found to be 79,250 per cubic millimeter, with 80% eosinophiles. The stools showed ova of T. trichiura, and the urine was normal. Intravenous injections of aminophylline and subcutaneous epinephrine afforded very little if any relief from the pulmonary distress. The symptoms continued unabated. On Sept. 29, 1950, x-rays of the chest revealed "diffuse parenchymatous infiltrations, with miliary nodules 1 to 3 mm. in diameter." On Dec. 4, 1950, the white blood cell count was 69,380 per cubic millimeter, with 91% eosinophiles. The increased severity of the pulmonary and systemic manifestations prompted the patient's admission to the hospital, on Jan. 15, 1951.

She had received 25 intravenous injections of oxophenarsine and 25 intramuscular injections of a bismuth preparation in 1946, because of a positive serologic test for syphilis. She lived in

a one-room apartment with her husband, who suffered from advanced pulmonary tuberculosis. There were no animal pets or flowering plants in or near her home. Hematological studies done on her brother, husband, and two of her children showed no abnormalities. However, a third child, massively infested with lumbricoides but otherwise healthy, showed an eosinophile count of 4,600. There was no family history of either asthma or any other form of allergy.

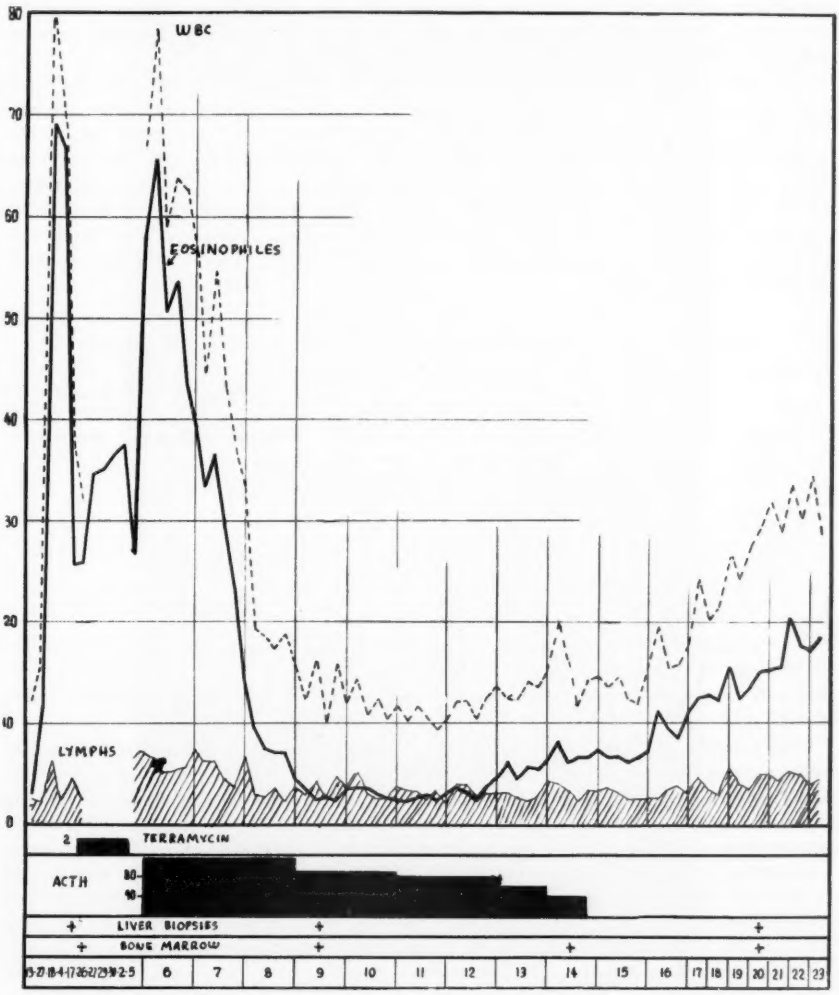

Fig. 1.—Effect of corticotropin on the total leucocyte, eosinophile, and lymphocyte counts.

She was poorly developed and poorly nourished and in no distress, with a temperature of 98 F., pulse rate 84, respirations 20 per minute, and blood pressure 120/84. The skin and lymph nodes were normal. The chest was symmetrical and slightly emphysematous, with many musical rales and wheezes. The heart appeared normal. The liver extended to 5 cm. below the costal border in the right midclavicular line, and the spleen was felt 2 cm. below the left costal border. Both organs were firm and nontender.

The hemoglobin varied from 64 to 84%; red blood cells, from 3,430,000 to 4,230,000 per cubic millimeter, and the volume of packed cells from 32 to 35 mm. The clotting and bleeding times were normal, and the sedimentation rate varied from 36 to 41 mm. in an hour. The platelet count was normal, and the blood serology test for syphilis was negative. Repeated icteric indices, sulfobromophthalein (Bromsulphthalein) excretion, cephalin flocculation, thymol turbidity, and prothrombin determinations were normal. Eight stool examinations revealed ova of T. trichiura, and several rectal biopsies and a skin test for Schistosoma mansoni were negative. The blood was free of microfilariae. The tuberculin patch test was positive; however, repeated sputum and gastric washings were negative for Mycobacterium tuberculosis.

The blood nonprotein nitrogen, urea, and creatinine were within normal limits. The blood uric acid varied from 3.14 to 6 mg. per 100 cc., and the total cholesterol, from 206 to 218 mg., with 17% of cholesterol esters. No eosinophiles were observed in the centrifuged urinary and spinal fluid sediments. The 17-ketosteroids, one week after corticotropin administration, were 20 mg. in 24 hours (upper limits of normal for females, 15 mg.). The total serum proteins were 6.9 gm. per 100 cc. of blood, with 3.2 gm. of albumin and 3.7 of globulin, on Feb. 15, 1951, whereas on March 25 the total was 7.3 gm., with 4.1 of albumin and 3.2 of globulin. The Widal, Weil-Felix, and Brucella agglutination tests and the cold hemagglutinin and heterophile antibody determinations were normal.

TABLE 1.—*Effect of Corticotropin on the Blood and Bone Marrow Eosinophiles*

Date	Blood Eosinophiles/ Cu. Mm.	Bone Marrow Eosinophiles, %		
		Myelocytes	Meta-myelocytes	Mature Cells
1/26/51	31,779	5	9	18
2/ 6/51	Corticotropin started	...	...	....
2/ 9/51	4,640	13	10.6	24
2/14/51	6,020	2.4	4.4	27.2
2/14/51	Corticotropin ended	...	...	....
2/20/51	29,900	6.6	2.0	44.2

The patient improved on supportive therapy within two days after admission, but on Jan. 17 to 19 she showed a low-grade fever (temperature reached 101 F.), which disappeared spontaneously. From Jan. 25 to Feb. 5 she received daily doses of 2 gm. of oxytetracycline (Terramycin) orally, without clinical or hematological improvement.

The patient received corticotropin (Armour) in daily doses of 120 mg. on Feb. 6, 7, and 8; 90 mg. on Feb. 9 and 10; 80 mg. on Feb. 11 and 12; 60 mg. on Feb. 13, and 40 mg. on Feb. 14 for a total of 800 mg. The hormone was administered in divided doses intramuscularly at six-hour intervals. Although four hours after intramuscular injection of 30 mg. of corticotropin or the subcutaneous injection of 1.0 cc. of aqueous epinephrine (Adrenalin) the level of circulating eosinophiles had not been altered, the initiation of therapy with corticotropin was accompanied by an initial rise followed by a steady and dramatic decline, to a level of 2,140 eosinophiles per cubic millimeter on the fifth day. A decrease in the dose of corticotropin to 20 mg. every six hours led to a steady increase of the circulating eosinophiles, to 30,000 per cubic millimeter 10 days after cessation of the therapy. The rise and fall of the total white cell count paralleled the changes in the levels of the circulating eosinophiles, with marked decline in lymphocytes (Fig. 1).

The number of eosinophilic elements in the bone marrow was unaltered by corticotropin therapy. They varied from 32% prior to the onset of therapy to 54% six days after its cessation. The proportion of eosinophilic myelocytes, metamyelocytes, and mature eosinophiles remained unaltered (Table 1). Serial x-ray studies of the lung failed to reveal beneficial alterations. Needle biopsies of the liver showed a heavy eosinophilic infiltration of the hepatic parenchyma and portal spaces prior to and after therapy, with practically complete disappearance of the infiltration during the administration of corticotropin, paralleling the decrease in the circulating eosinophiles (Fig. 2, 3, and 4).

With eosinophile levels of 26,740 per cubic millimeter, the patient received 0.5 cc. of triple typhoid vaccine ‡ containing 500,000,000 Salmonella typhosa and 250,000,000 Salmonella paratyphi A and B organisms, on Feb. 26. Although induration and redness appeared at the site of the

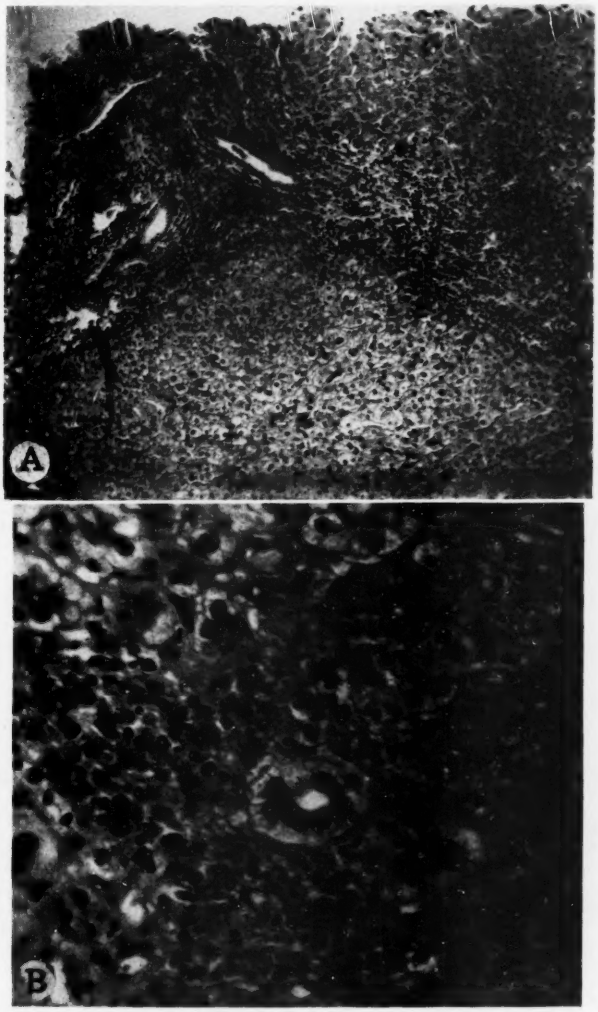

Fig. 2.—*A*, needle biopsy specimen of liver prior to corticotropin therapy, showing periportal eosinophilic and lymphocytic infiltration; × 80. *B*, the same, showing a periportal space with eosinophilic and lymphocytic infiltration; × 360.

injection, the patient remained afebrile, and the eosinophile counts, done every two hours, remained unaltered. Identical results were recorded when twice that amount of vaccine was administered on the next day.

‡ Lederle Laboratories Division, American Cyanamide Company, Pearl River, N. Y.

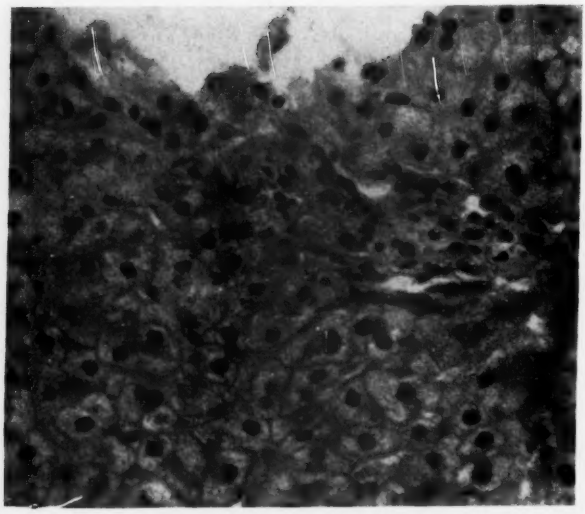

Fig. 3.—Needle biopsy specimen of liver during treatment with corticotropin, showing marked decrease of infiltrating eosinophiles and lymphocytes in periportal space; × 360.

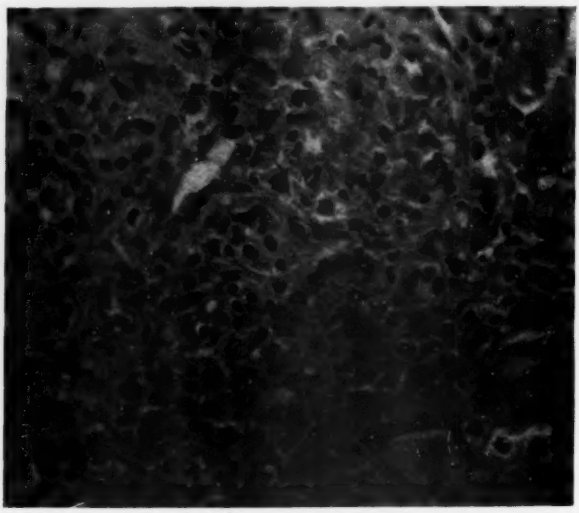

Fig. 4.—Liver biopsy specimen after treatment with corticotropin and before treatment with arsenic, showing reappearance of eosinophilic and round cell infiltration; × 360.

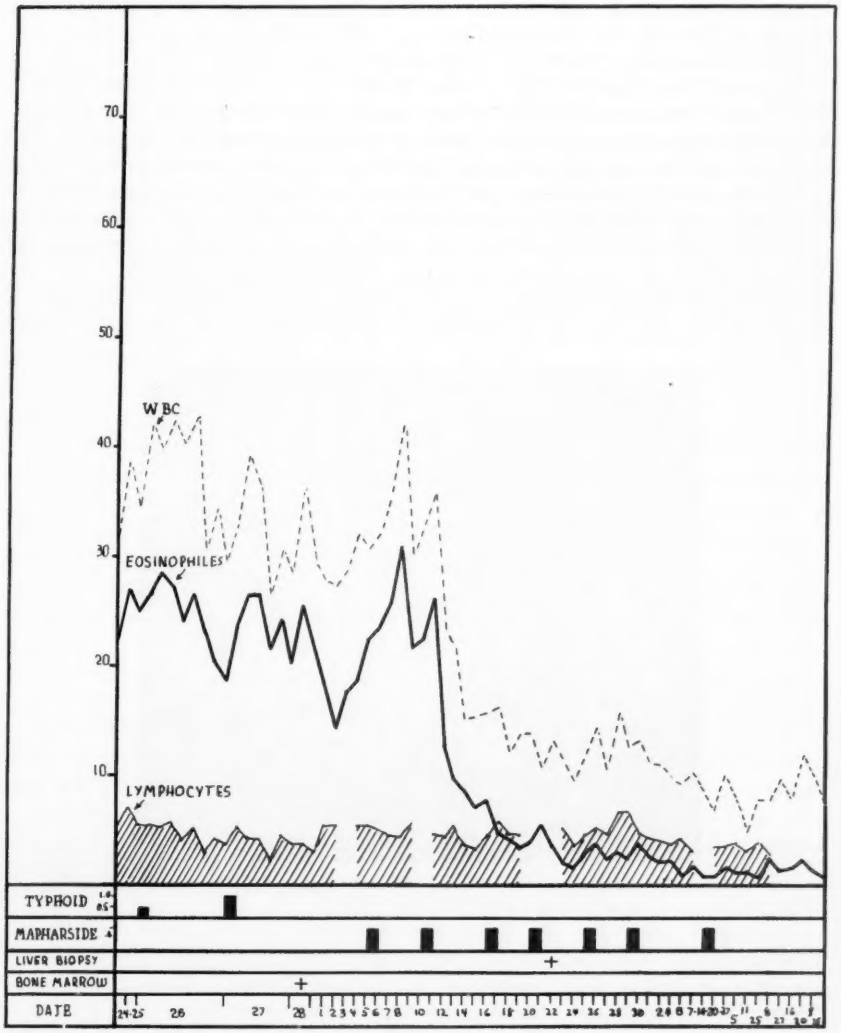

Fig. 5.—Effect of oxophenarsine (Mapharsen) on the total leucocyte, eosinophile, and lymphocyte counts.

TABLE 2.—*Effect of Arsenic on the Blood and Bone Marrow Eosinophiles*

Date	Blood Eosinophiles/ Cu. Mm.	Bone Marrow Eosinophiles, %		
		Myelocytes	Meta-myelocytes	Mature Cells
2/28/51	25,540	6.0	4.0	44.0
3/ 5/51	Arsenic started	...	...	....
3/13/51	9,820	2.5	2.0	42.0
4/ 7/51	1,600	3.5	1.0	8.0
4/26/51	Arsenic ended	...	...	....
6/ 4/51	2,520	1.5	3.0	3.5
1/ 9/52	960	0.5	0.5	1

Treatment with 0.04 gm. doses of intravenous oxophenarsine hydrochloride (Mapharsen§) every five to seven days were initiated on March 5. A rapid fall in the number of circulating eosinophiles, from 22,300 to 12,975, was noted within five days. However, permanent normalcy was not attained until April 14 (Fig. 5). With the decrease in circulating eosinophiles, there was a significant diminution in the eosinophilic elements of the bone marrow, from 46.5% to 12.5%, within 30 days after the initiation of therapy (Table 2). A relative lymphocytosis and decrease in circulating neutrophiles was also observed, with a return to normal after treatment.

Seventeen days after the administration of arsenic a liver biopsy showed definite periportal fibrosis and marked diminution of infiltrating eosinophiles (Fig. 6).

Since her discharge from the hospital the patient has suffered repeatedly from allergic rhinitis. In spite of two severe respiratory infections, there were no signs of asthma. The spleen progressively returned to normal and has not been palpable since November, 1951, and the liver can now be felt 2 cm. below the costal margin. A thorough study by the allergist || revealed

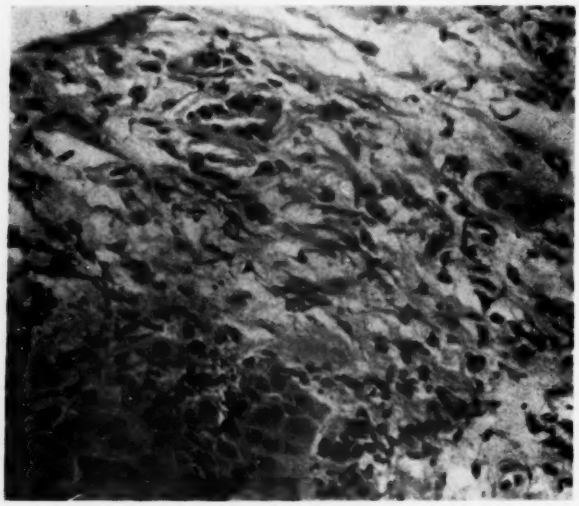

Fig. 6.—Liver biopsy specimen after treatment with arsenic, with moderate increase of the periportal fibrosis without eosinophilic infiltration; × 360.

hypersensitivity to house dust. Serial roentgenologic studies of the lungs show progressive clearing of the nodular miliary infiltrations, with definite evidence of fibrosis. Only stellate lesions with small dense centers and fine converging strands now remain.

COMMENT

It is recognized that eosinophilia may accompany various allergic conditions, dermatoses, infections, parasitic infestations with invasion of tissues, blood dyscrasias, Hodgkin's disease, malignant diseases, bone diseases, splenectomy, irradiation, the administration of some drugs, and the collagen disorders. However, in infiltrative eosinophilia eosinophilic leucocytosis is not a collateral or incidental finding but a *sine qua non* for its recognition.[89]

§ Parke, Davis & Company, Detroit.

|| Dr. Angel Marchand, Consultant in Allergy, San Juan City Hospital, cooperated in the study of this case.

With our expanding knowledge of tissue response in the hypersensitive state, it now appears that conditions believed to be distinct entities are so closely related that they seem to be gradients or variants of the same state.¶ The nature and intensity of the clinical manifestations are governed by the extent of the allergic reaction and the organ or organs predominantly affected. Thus, antigen-antibody reactions manifested as asthma, periarteritis nodosa, rheumatoid arthritis, rheumatic carditis, and transitory pulmonary eosinophilic infiltration, with the most prominent clinical manifestations referred to the most severely affected organ, have been reported in the same patient.[85] There is experimental proof to show that lesions of periarteritis nodosa, rheumatic fever, and acute glomerulonephritis may appear together in rabbits given desoxycorticosterone # and that pulmonary lesions comparable to those of rheumatic fever may appear in the sensitized experimental animal after the intravenous injection of foreign protein. A high incidence of bronchial asthma (18 to 25%) has been reported among those cases of severe periarteritis nodosa that are accompanied by high eosinophile levels.[84]

The hypersensitivity state is reversible during the early stages, as is exemplified by Loeffler's syndrome. However, continued or repeated antigen-antibody reactions may result in chronic inflammatory alterations with irreversible tissue changes, as those observed in classical periarteritis nodosa or in the so-called tropical eosinophilia. The accompanying manifestations of pericarditis, peritonitis, and pleurisy, as well as the hepatic and lymph node involvement, with extensive vascular damage, in Loeffler's syndrome, would suggest that in some instances this allergic state may be extremely severe and generalized.* The close similarity between the vascular alterations in Loeffler's syndrome and those of periarteritis nodosa lends support to the theory of a common pathogenesis.[85] The possible relationship between the hypersensitivity states in trichinosis and in periarteritis nodosa has been suggested.[86] If a bond could be established between periarteritis nodosa and the hypersensitivity state induced by the close contact of parasites or their ova with the host's tissues, it could be speculated that classic periarteritis nodosa is the end-result of a continuous, unrelenting reaction of the tissues to any of multiple and variable allergens and that chronicity, with irreversible tissue alterations, is only reached after previous stages during which the disease remained unrecognized.

Although many cases of infiltrative eosinophilia are associated with parasitic infestations, there are some without any as yet recognizable cause. The probability of a parasitic causation appears eliminated by the unaltered persistence of symptoms after the eradication of the parasites and by the prompt disappearance of symptoms after arsenical therapy. This would suggest a rare form of allergy amenable to arsenic. It has been demonstrated that severe infiltrative eosinophilia resulting from acute schistosomiasis, ascariasis, and uncinariasis does not respond to arsenicals.†

The gross and histologic pulmonary alterations and the invariably constant failure of response to aminophylline, epinephrine, and iodides would suggest that infiltrative eosinophilia is pathogenetically somewhat different from spasmodic bronchial asthma. Although the possibility of a bacterial causation cannot be entirely dismissed, the ineffectiveness of most of the antibiotics (penicillin, streptomycin,

¶ References 90-98.

References 96-98.

* References 82 and 83.

† Díaz-Rivera, R. S., and Ramos-Morales, F.: Unpublished data.

chlortetracycline [Aureomycin], oxytetracycline) and chemotherapeutic agents (sulfadiazine) is evidence in support of a different causation. However, bacterial allergy should be considered as a probable underlying factor.

The exact mode of action of arsenic is impossible to assess. Although this drug promptly relieved the symptoms in our cases, still the reduction of the eosinophile count was delayed, and at times normal levels were not reached for several weeks or months. The increase in the severity of symptoms, with an almost constant increase in the eosinophiles after the initial dose of arsenic by vein, suggests either stimulation of the bone marrow, with overproduction of these cells, or their mobilization from infiltrated areas throughout the body. Some observers have suggested the possibility of massive destruction of eosinophiles, with an excessive production of histamine, to explain this phenomenon.[40] However, massive destruction without mobilization or overproduction fails to explain the increase in circulating eosinophiles. If the intensification of symptoms were due to massive destruction, chronicity should be maintained with the more marked dissolution observed during weeks and months following the initiation of therapy, until the hemogram reaches normal values.

Evidence is presented here and elsewhere [6] to suggest that there is rapid dissolution of the circulating and infiltrating eosinophiles, following the transitory initial elevation, after the administration of arsenic and that bone marrow depression in the production of this cell is delayed. Although the period of administration of corticotropin was perhaps limited and the doses were small, a definite destruction of eosinophiles was observed without alteration of the eosinophilic population of the bone marrow. It seems that arsenic and corticotropin behave similarly in relation to the effect on the circulating and infiltrating eosinophiles but have different effects on the bone marrow. More prolonged schedule and heavier doses of corticotropin might have yielded different results.

Whether the effects of corticotropin and of arsenic in the circulating or infiltrating eosinophile are governed by the same mechanism remains a moot question. There is evidence to suggest that both drugs alter cellular function by paralysis of the S-H groups.‡ However, the failure of arsenic to alter the blood eosinophile values in acute parasitic infestations would favor other mechanisms.

Even if it is accepted that arsenic is lethal to an existent causative organism, its mechanism of action is unexplained and infiltrative eosinophilia remains in the allergic circle. However, it is known that arsenic may inhibit the formation of leucocytes when this is excessive. It is stored in the liver, spleen, kidney, walls of the gastrointestinal tract, muscles, lungs, etc., and, although its excretion may start within two to eight hours, complete elimination may be prolonged for as long as 10 days after a single dose and as long as 70 days after repeated administration.[100] The storage of arsenic may explain the slow, continuous, and invariable reduction of eosinophiles after the completion of therapy extending for as long as four months.

The rapid return of lung, lymph nodes, liver, and spleen to normalcy observed in some of the acute cases following arsenical therapy remains unexplained. It can be suggested that rapid beneficial effects resulted from mobilization and lysis of the eosinophiles from the infiltrated organs, following the removal or alteration of the underlying cause, in conjunction with the later depression of the bone marrow limiting the production of this type of cell. Complete recovery may only occur after

‡ References 99 and 100.

the correction of the pathologic process before the severest, irreversible stages of the hypersensitivity state are reached. It can also be speculated that the immediate beneficial effect derived from arsenic may be due to rapid improvement in the pathologic process and that recovery is attained only after disposal of the causative factor through an immunologic response of the body.

The lysis of the infiltrating eosinophiles may not be curative, as is exemplified by one of our patients,[21] in whom the pulmonary symptoms have persisted unabated for more than four years, in spite of a normal hemogram. It appears that this patient suffered from spasmodic bronchial asthma of a different pathogenesis. The underlying cause of this phenomenon may have been irreversible damage to the bronchial tree or permanent sensitization to another allergen.

SUMMARY

An attempt is made to group all conditions characterized by a relative and absolute increase in the circulating mature eosinophiles and an inflammatory reaction of tissues with this cell under the term infiltrative eosinophilia.

The clinical data from a case of infiltrative eosinophilia with symptoms referable to the lungs and with hepatic, splenic, and bone marrow involvement are presented. Reference is made to our series of 30 cases under study.

Treatment with corticotropin led to a rapid but transitory dissolution of circulating eosinophiles and of those infiltrating the liver and lungs. This was accompanied by transitory improvement in the clinical picture, but the eosinophilic population of the bone marrow remained unaffected.

Intravenously administered arsenic led to a less dramatic decrease in circulating and infiltrating eosinophiles, with a return of the bone marrow to normalcy.

The beneficial effects and the mechanism of action of arsenic in some instances of infiltrative eosinophilia remain unexplained.

Enough evidence has been collected from studies in experimental animals and man to demonstrate the essential similarity of tissue response in some instances of infiltrative eosinophilia and periarteritis nodosa.

Infiltrative eosinophilia appears to be a phase, modality, stage, or gradient of a hypersensitivity state whose clinical manifestations depend on the degree of tissue reactivity, nature and intensity of the stimulus, and diffusedness of the susceptible field.

The tissue reactions may be transitory, chronic, recurrent, or irreversible.

Infiltrative eosinophilia remains in the group of allergic diseases, deserving further investigation.

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Dr. E. Koppisch, Professor of Pathology of the School of Medicine of the University of Puerto Rico made the interpretations of the liver biopsy sections.

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NEUROGENIC HYPERTENSION IN MAN IN PORPHYRIA

Transient Hypertension and Tachycardia Caused by Disruption of the Carotid Sinus; Review of Buffer Nerve Mechanism

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NORMAL blood pressure has a very sensitive adaptability to the demands of the circulation mediated through the reflex system of the carotid sinus and aortic nerves. Physiologists envision normal blood pressure as a balance between two forces: intrinsic vasomotor tone on one hand and constant counteraction of the sinoaortic regulatory system on the other. Superimposed upon the vasomotor center in the medulla there are higher coordination centers of the circulation in the hypothalamus. W. R. Hess distinguishes two parts of the hypothalamic circulatory center, a posterior and an anterior part. In the cat, electrical stimulation of the former leads to blood pressure rise and tachycardia; stimulation of the latter leads to blood pressure fall and pulse rate decrease.[1] Bronk and co-workers found that, depending on the frequency of stimulation, the same area can give either result.[2] They concluded that hypothalamic activity regulates the effectiveness of the afferent inhibitor impulses from the buffer nerves. Blood pressure and cardiac function, however, are still maintained after removal of the hypothalamus. The vasomotor center in the medulla consequently can maintain its tone independently from the hypothalamus. The same is true for the buffer mechanism. The buffer reflexes are still effective in decerebrate animals. The hypothalamus probably functions in coordination and mediation between cortical impulses and their effects on the circulation.

The aortic and carotid sinus nerve receptors are stimulated by the pulsatile expansion of the arterial walls. The impulses are carried in the afferent pathways of the medullated carotid sinus and aortic nerves, which join the glossopharyngeal or the vagus nerves, respectively. They end in the bulbar centers, i. e., in the reticular formation and in the dorsal nucleus of the vagus. From here the inhibitor impulses are distributed to the neighboring vasomotor center and to the hypothalamic circulatory center.

The physiological tone of the vasomotor center is set at a higher level than is actually found in normal blood pressure, but it is constantly counteracted by the carotid sinus and vagiaortic nerve mechanism. Constant inhibitor impulses travel from the barosensitive arteries to the centers even in resting blood pressure and pulse rate levels, as was demonstrated by Bronk and Stella by registration of the action potential of the carotid sinus nerves.[3] Thus, the disruption of these nerves results in sudden and marked tachycardia and in constant hypertension which rep-

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resents the uninhibited tone of the vasomotor center. Evidence suggests that the tone of the vasomotor center is maintained by the inflow of peripheral impulses originating in the special sense organs and the cortex and in endocrine-metabolic functions (Kennedy and Osborne [4]). The sum of these impulses is excessive, but the constant inhibition of this physiologically high tone by the buffer mechanism results in normal blood pressure and pulse rate.

STUDY OF FUNCTION OF SINOAORTIC REGULATORY SYSTEM

Despite the extensive studies of physiologists, the function of the sinoaortic regulatory system in abnormal elevations of the blood pressure is not well understood. Few investigators of the pathogenesis of hypertension have concerned themselves with the question of why hypertension is not counteracted by this sensitive regulatory system.

To investigate this question it is necessary to have an accurate test of the functional state of the buffer nerve system. In animal experiments direct stimulation and the disruption of these nerves (also occlusion of the common carotid arteries in the case of the carotid sinus) are used for this purpose. Each animal species reacts to stimulation with a certain degree of blood pressure fall and with slowing of the pulse rate, while disruption of the nerves results in a certain degree of blood pressure elevation and pulse rate increase. In humans stimulation of the carotid sinus is accomplished by pressure over the carotid bulb. However, a test for disruption was not available. For this purpose transient disruption of the carotid sinus by procaine block was devised, and the results obtained in normotensive and hypertensive humans have been reported in previous publications.* With these two tests, the functional state of the carotid sinus can readily be determined. Normotensive persons react in a manner similar to the response in experimental animals. Hypertensive persons react in three different ways. It was concluded that the functional state of the carotid sinus in hypertension can be classified in one of three groups (Chart 1).

Group I. Normal Functional State.—This group includes patients with essential, malignant, and chronic nephritic hypertension. These patients responded to procaine block with the same degree of pulse rate increase and blood pressure rise as do normotensive subjects, merely starting from a higher level initially. Pressure over the carotid bulb produced a drop in pressure which was quantitatively similar to that in normal persons. Resting pulse rate and cardiac output in these patients are normal. It has been proposed that the apparent new balance of the regulatory system at a higher blood pressure results from loss of elasticity of the barosensitive arterial walls. This, in turn, results in disturbed pulsatile expansion and in decreased stimulation of the pressoreceptors.[7] Blood pressure is then raised, through peripheral vasoconstriction, to a level which results in normal stimulation of the receptors. Peripheral vasoconstriction then leads to generalized secondary arteriolar changes, and the hypertension becomes fixed.

Group II. State of Abnormally High Stimulation.—This occurs in acute glomerulonephritis [8] and, experimentally, by infusion of renin, hypertensin, or arterenol (Nor-epinephrine) in normal humans.[9]

* References 5 and 6.

In these conditions resting cardiac output is rather low, and there is a bradycardia resulting from reflex inhibition by the highly stimulated buffer nerves. However, an elevated blood pressure is maintained by a humoral agent (renin) in spite of the depressor reflexes.

Since the pressor receptors are already maximally stimulated, external pressure over the carotid bulb produces no change either in pulse rate or blood pressure. Procaine block results in unusual response. The bradycardia is abolished, and pulse rate increases to a rate equal to that reached by normal persons after procaine block. Blood pressure is increased only up to the level reached by normal patients

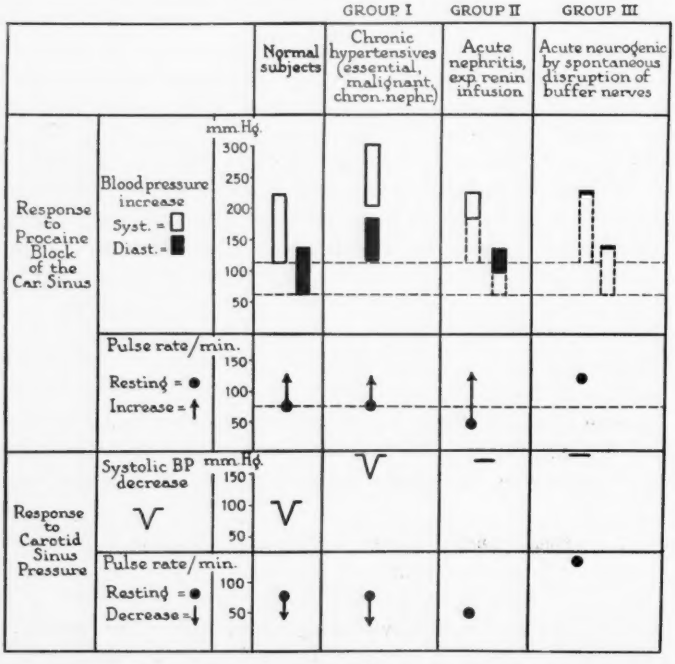

Chart 1.—Response of the blood pressure and pulse rate to procaine block and digital pressure of the carotid sinus in normal and hypertensive subjects (Average values of peak levels).

following procaine block. Thus, there is a much higher percentage rise in pulse rate than in blood pressure. This discrepancy is explained by the fact that peripheral vasoconstriction is already maintained near maximal capacity of a normal vessel system by the humoral agent, leaving little more to be accomplished by the nervous system.

Group III. Disruption of Buffer Nerves.—It was found that, in polyneuritis, transient hypertension and tachycardia can develop if the glossopharyngeal and vagus nerves are involved. The carotid sinus and aortic nerves, since they are carried in the glossopharyngeal and vagus nerves, can also be disrupted by the

neuritic process. This would result in uninhibited central vasomotor tone. Carotid sinus pressure and procaine block in these patients would have no results. These tests were performed in only 1 of 10 cases reported by Lampen.[10]

REPORT OF A CASE

Recently we had the opportunity to study a patient with polyneuritis caused by idiopathic porphyria.

A 24-year-old married woman was admitted to Wesley Memorial Hospital for the first time in August, 1951. The patient complained of severe abdominal pains which had occurred intermittently for three days. She also had complaints of numbness in her hands. She had taken barbiturates previously for pain without improvement.

The physical examination showed normal internal organs. The reflexes were equal and of normal intensity. The right hand was somewhat weaker than the left. There were no sensory changes or nuchal rigidity. Pupils were somewhat constricted but responded well to light. The fundi were normal. Laboratory findings showed blood NPN, creatinine, sugar, and CO_2-combining power to be normal. The urine was dark red, with no pathological findings on micro-

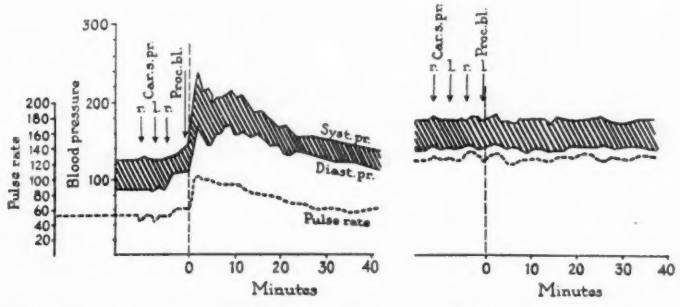

Chart 2.—Course of the blood pressure and pulse rate following carotid sinus pressure and procaine block of the carotid sinus in a normal person and in the patient with spontaneous disruption of the carotid sinus nerves in prophyria. Car. s. pr., carotid sinus pressure; Proc. bl., procaine block; r, right; l, left.

scopic examination. A test for porphobilinogen was strongly positive. The blood pressure was 130/80, and the pulse rate was 75 per minute.

In the following eight days the patient developed progressive neurological symptoms. She complained of severe pains in her arms and shoulders and later showed weakness of both hands which progressed to complete wrist drop. There was also weakness of the shoulder girdle, of the triceps muscles, and of the hip girdle. Later, deviation of the tongue to the right developed. With these neurological symptoms the pulse rate increased to 110 to 120 per minute, and the blood pressure increased to 150/100. Following improvement of the neurological state, two weeks after admission, the blood pressure and the pulse rate returned to 120/80 and 66 per minute. Examination of the family showed that one sister had porphobilinogen in her urine, without symptoms.

During a second admission, in March, 1952, the patient developed paralysis of the extensors of the fingers and had severe pains in her arms. The urine showed strong reaction for porphobilinogen. For a short time she had some difficulty in swallowing. The blood pressure rose from 122/90, on the admission day, to 144/100, on the fifth day. The pulse was around 110 per minute. She was given meperidine (Demerol) for pain and a trial with hexamethonium, 75 mg. twice a day, for eight days. The blood pressure dropped suddenly after the first dose to shock levels but then rose gradually and remained normal. The neurological symptoms improved rapidly this time, and the pulse rate and blood pressure were normal on the day of discharge.

The third admission was in March, 1953. This time abdominal pains, nausea, and vomiting introduced the attack. The urine was dark red, and a test for porphobilinogen was strongly positive. No abnormal neurological findings were present on the day of admission. During this admission the functional state of the carotid sinus was frequently tested. The blood pressure was 114/68 and the pulse rate was 70 per minute on the day of admission. On the fifth day the patient complained of severe pains in both arms and legs. The right eye showed weakness of the lateral rectus, and she had double vision. A slight nystagmus was present. No other cranial nerves were involved. The blood pressure was 120/90, and the pulse rate was 90 per minute. Pressure on the carotid sinus bulb bilaterally resulted in a definite slowing of the pulse rate, from 90 to 60 per minute on the right side and to 66 per minute on the left. Two days later the patient had convulsions which lasted about two minutes. The neurological examination then showed bilateral wrist drop. Right abducens paralysis and nystagmus were still

Response of the Pulse Rate to Carotid Bulb Pressure in a Case of Idiopathic Porphyria with Hypertension and Tachycardia in Different Stages of the Disease (Pulse Recorded by ECG)

Date	Blood Pressure, Mm. Hg	Pulse Rate/Min.	Carotid Sinus Bulb Pressure Test: Side	Decrease of Pulse Rate to Beats/Min.	Duration of Pulse Rate Slowing, Sec.	Remarks
3/12/53	125/90	90	Rt	60	8	No bulbar symptoms
		90	Lt	66	6	
3/17/53	170/120	130	Rt	No response	—	Symptoms of glossopharyngeal paralysis
		130	Lt	No response	—	
3/19/53	170/125	120	Rt	No response	—	No further blood pressure elevation after procaine block of carotid sinus
		125	Lt	No response	—	
3/21/53	140/100	115	Rt	80	6	Symptoms of glossopharyngeal paralysis improved; hoarseness
		120	Lt	No response	—	
3/23/53	134/98	120	Rt	100	4	.....
		120	Lt	No response	—	
3/26/53	138/106	120	Rt	100	4	No symptoms of glossopharyngeal paralysis; hoarseness; dysphagia
		120	Lt	98	6	
4/ 1/53	120/100	120	Rt	95	6	.....
		115	Lt	100	5	
4/16/53	130/90	110	Rt	85	4	No symptoms of paralysis of the 9th and 10th cranial nerves
		105	Lt	80	6	

present. The uvula deviated to the left, the gag reflex was diminished, and fluids came back through the nose on swallowing. Reflexes were diminished but equal. The circumscribed paralysis of the hands without sensory changes suggested anterior horn lesions rather than peripheral neuritis. The incomplete paralysis of the 9th and later of the 10th cranial nerves and the eye symptoms were also more likely central in their origin. The blood pressure rose after the attack to 170/132, and the pulse rate rose to 120 to 130 per minute and stayed at this level for five days. Repeated pressure tests on the carotid sinus during this period showed no changes in pulse rate or blood pressure. Procaine block of the carotid sinus performed on the third hypertensive day did not lead to further blood pressure or pulse rate elevation. Chart 2 shows the response of a normal subject compared with the negative effect to procaine block in this patient. The Table gives the response of the carotid sinus to digital stimulation in the different stages of the blood pressure elevation. On the fifth day after the attack the blood pressure dropped to 130/100 and the pulse rate decreased to 115 per minute. The carotid sinus then showed response to pressure on the right side only. With gradual decline of the blood pressure the carotid sinus pressure test became effective again on both sides.

During the gradual decrease of the blood pressure the neurological symptoms changed. The deviation of the uvula and the paralysis of the palatine arch were not present, and the gag reflex became normal again. However, hoarseness developed, which lasted for several days. The short symptoms of glossopharyngeal paralysis were replaced by a more extensive involvement of the vagus. During this time the blood pressure and the pulse rate remained somewhat elevated. After a long and gradual recovery all the cranial nerve symptoms returned to normal. The paralysis of the hands and fingers made only slow progress toward improvement. The blood pressure and the pulse rate returned to normal, and the carotid sinus pressure test was always positive after cranial nerve recovery. A procaine block of the carotid sinus was not repeated in this stage, because sudden blood pressure elevation was not desirable after the previous long strain on the heart.

COMMENT

Hypertension and tachycardia are common findings in the polyneuritic form of idiopathic porphyria. There are different theories about the pathogenesis of this blood pressure elevation. Waldenström,[11] Vanotti,[12] and others think that porphyrin has a stimulative effect on the sympathetic nervous system. Nesbitt [13] suggests an arteriospastic origin of the high blood pressure. Nesbitt's patient had dysphagia, and the gag reflex was absent during the hypertensive phase. The patient of Baker and Watson [14] had a blood pressure elevation of 180/120 mm. Hg combined with tachycardia while dysphagia, disturbed speech, and deviation of the tongue developed. The postmortem examination showed neuronal and myelin sheath alterations in the central nervous system. These pathological changes were most marked in the dorsal nucleus of the vagus, in the reticular formation, and in the facial and hypoglossal nerve nuclei.

In our case the blood pressure rose only when symptoms of glossopharyngeal or vagal nerve impairment developed. During the third attack blood pressure and pulse rate were still normal when other extensive paralytic symptoms developed in the upper extremities and paralysis of only the right sixth cranial nerve was present. The carotid bulb pressure test showed that both carotid sinus nerves were functioning at this time. When the cranial nerve impairment extended to the glossopharyngeal nerve, the blood pressure and the pulse rate suddenly rose to high levels. Neither the carotid pressure test nor the procaine block were positive at this stage. The conclusion is, therefore, that the carotid sinus nerves were paralyzed together with the glossopharyngeal nerves and that their inhibitory mechanism was suspended. If the hypertension were caused by direct sympathetic center stimulation or direct arteriolospasm, one could not understand why the blood pressure rose only after the 9th and/or 10th cranial nerves became paralyzed. The toxic effect of porphyrin on the sympathetic center and the arterioles was already present when the upper extremities and the abducens nerve were involved, and yet the blood pressure was normal. The pressure test on the carotid sinus, when previously positive, should also not be altered during the hypertensive phase if direct sympathetic stimulation is the cause of blood pressure rise. In our case the carotid bulb could easily be felt through the thin neck of the patient, and the condition for adequate stimulation of the carotid sinus was always good. The test was repeated several times with the same result. Furthermore, the procaine block of the carotid sinus did not lead to further blood pressure and pulse rate increase, thus proving their disruption by the neuritic process.

The degree of blood pressure elevation and tachycardia depends naturally on the extent of the involvement of the nerves. Experimental disruption of each buffer

nerve separately results in a moderate degree of blood pressure and pulse rate elevation. Cutting all four buffer nerves in acute animal experiments results in a systolic blood pressure rise of 120 to 140 mm. Hg.[15] Later, during the stage of chronic disruption, the blood pressure gradually decreases to a somewhat lower level than the peak following acute disruption but is then very labile.

The moderate blood pressure elevation in our case is explained by two factors. First, the blood pressure elevation is of the type seen in chronic disruption of the buffer nerves. Second, all four buffer nerves were not paralyzed at the same time. The initial blood pressure rise was accompanied only by symptoms of glossopharyngeal paralysis. The secondary rise in pressure was accompanied by symptoms of vagal paralysis. However, at this time the function of one sinus nerve and, shortly thereafter, that of the other sinus nerve returned. This was proved by the carotid bulb pressure test.

The pathological findings of Baker and Watson [14] suggest that the function of the sinoaortic regulatory system can even be suspended in the centers themselves, since the fibers of the buffer nerves terminate in the reticular formation and in the dorsal vagal nucleus, which showed the greatest damage in their case. In addition to the centers of the buffer nerves, the neighboring vasomotor center itself can be involved.

The above-suggested mechanism can probably initiate transient hypertension in polyneuritis and polyradiculitis (Guillain-Barré syndrome) of other etiology than porphyria if the 9th and 10th cranial nerves are involved in the process. In fact, there are observations of transient hypertension with tachycardia during the course of rheumatic,[16] postdiphtheritic,[10] and toxic (thallium) [17] polyneuritis. Patients with tuberculous meningitis can develop hypertension if the process involves the cranial nerves at the base of the skull.[18]

Hypertension and tachycardia in bulbar poliomyelitis have also been observed and discussed by several authors. According to some reports, 50 to 70% of patients with bulbar poliomyelitis develop hypertension and tachycardia, which last from a few days to several weeks.† In nonparalytic or spinal cases the incidence of hypertension and tachycardia is as low as 5 to 10%. In bulbar poliomyelitis histological alterations of the medullary centers similar to those in porphyria were shown by Baker and associates.[21] This would suggest a mechanism of hypertension in this disease similar to that in porphyria. However, the proof of this concept requires more extensive study of the carotid sinus by the function tests described. It is hoped that this study of carotid sinus function in porphyria will direct attention to the possibility of true neurogenic hypertension in man resulting from disruption of the inhibitor nerves.

SUMMARY AND CONCLUSIONS

From previous studies of the functional state of the carotid sinus in normal persons and in patients with different types of hypertension it was concluded that hypertension can be classified in these three groups:

1. Hypertension in which the sinoaortic system is adapted to the blood pressure elevation by loss of elasticity (or disturbed pulsatile expansion) in the barosensitive vessel system. Characteristics are normal pulse rate, normal cardiac output, and high peripheral resistance, combined with loss of elasticity of the large vessel system.

† References 19 and 20.

The pressure test on the carotid bulb and the procaine block of the carotid sinus show the same degree of response as in normal persons. Examples are essential, malignant, and chronic renal hypertension.

2. Hypertension in which the sinoaortic system is markedly stimulated and its functional potency is fully exhausted in attempt to lower the elevated blood pressure. Characteristics of this hypertension are bradycardia and extremely high peripheral resistance. The carotid sinus shows no response to the pressure test and an unusual response to procaine block. Examples of this hypertension are that of acute glomerulonephritis and experimental hypertension caused by humoral agents such as renin, arterenol (Nor-epinephrine), and, probably, cerebral vasopressor substance.

3. Hypertension in which the sinoaortic nerves are partly or totally disrupted by pathological processes involving their peripheral routes or their centers. Characteristics of this hypertension are extreme and permanent tachycardia, high cardiac output, and moderately high peripheral resistance. There is no response either to carotid sinus pressure or to procaine block, because the nerves are already disrupted.

Evidence has been presented for temporary suspension of the inhibitory function of the carotid sinus nerves, leading to transient hypertension, in a case of polyneuritis in porphyria with symptoms of partial glossopharyngeal and vagal nerve paralysis. On the basis of pathological findings of other authors in studies of porphyria with bulbar symptoms and hypertension, it is suggested that not only peripheral neuritis but also involvement of the medullary inhibitory centers can lead to transient hypertension and tachycardia. The narrow course of the four buffer nerves and the relatively small area of the inhibitory centers condensed in the ventromedial part of the reticular formation and in a small part of the dorsal nucleus of the vagus account for the vulnerability of this system.

Analogous histological findings in bulbar poliomyelitis suggest that hypertension and tachycardia in the course of this disease have the same mechanism as in porphyria. Hypertension, shock levels of blood pressure, and circulatory paralysis are probably the results of the same damaging process, depending on which part of the centers is involved, the inhibitory or the vasomotor.

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QUINACRINE (ATABRINE) IN TREATMENT OF SYSTEMIC AND DISCOID LUPUS ERYTHEMATOSUS

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LOS ANGELES

PROKOPTCHOUK, in 1940, introduced the use of quinacrine (Atabrine; Mepacrine) for discoid lupus erythematosus,[1] and Popoff [2] reported similar success. Since the recent report by Page,[3] there has been a flurry of confirmatory studies.* One of the patients in Page's series had active systemic lupus, which responded well to 200 mg. of quinacrine daily. In view of this and the fact that there is excellent evidence that systemic lupus erythematosus is a malignant form of the discoid variety, it seemed important to study the use of quinacrine in the generalized form of the disease.‡ Initial studies, in 1952, on three patients with acute systemic lupus erythematosus, using the dose recommended by Page, 200 mg. per day, showed no effect on the disease. The drug was not employed again until further confirmatory reports on its use in the discoid form of the disease appeared. It then seemed that if this substance was effective in the local variety of the disease it might be useful in the systemic form in much larger doses, in view of the fact that the amounts of corticotropin (ACTH) or cortisone needed to produce a remission varied with the severity of the disease.[11] Simultaneous studies were begun with patients and in the laboratory to study the possible effect of quinacrine on the L.E. phenomenon in the test tube.

This report deals with the clinical studies on 22 patients, 20 with systemic lupus erythematosus and 2 with the discoid form. The experimental in vitro results will be fully discussed in another paper.[12] Preliminary tests show that quinacrine inhibits the L.E. phenomenon in vitro in a concentration of 20 mg. or more per 100 cc. and that it does this without killing the leucocytes and thereby blocking the L.E. reaction.

MATERIALS AND METHOD

Quinacrine dihydrochloride in plain and sugar-coated tablets was given to the patients in initial doses varying from 1 mg. per day, in a patient who was known to be sensitive to the drug, to a maximum initial dose of 600 mg. per day. An attempt was made to gradually increase the drug to the point of clinical improvement or toxicity. If gastroenteritis appeared, the dosage was decreased temporarily. However, if a dermatitis or psychosis appeared the drug was permanently discontinued. The outpatients were examined at intervals of one week for evidence of toxicity. Hemoglobin and white blood cell counts were performed each time until a quinacrine maintainance-level had been established, and then these counts were performed at two-week intervals. Plasma quinacrine levels were determined by the method described by Brodie and Udenfriend.‡

RESULTS OF CLINICAL STUDIES

Twenty-two patients have been treated to date (see Addendum). In order to correlate the results into a comprehensive pattern, it is worth while to group lupus

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* References 4-8. † References 9 and 10. ‡ Reference 13. These determinations were performed at Bio-Science Laboratories, Beverly Hills, Calif.

erythematosus patients into four divisions, according to the severity of the disease, which may be rated as 1 + to 4 + (Table 1).

Patients with discoid lupus are those with classic indurated erythematous scaling lesions, which are usually limited to the face and which appear and disappear for many years. There is no arthralgia, leucopenia, fever, or abnormalities in the liver-function studies. The sedimentation rate is normal or low. In other words, there is no evidence by any test of dissemination. The severity of the disease in these patients may be graded as 1 +. The two patients in this group, as outlined in Table 1, had complete healing of the skin lesions in three to four weeks. These results are similar to those of other series (see Addendum).

Patients with chronic systemic lupus erythematosus may be defined as those who have the typical discoid-like lesions, which often appear not only on the face but on the upper extremities and V-area as well. In addition, there are flare-ups of systemic involvements, as indicated by arthralgia, low-grade fever, and abnormal liver-function tests. The arthralgia may also be persistent and resemble a rheumatoid arthritis. The L.E. test, however, is negative. The four patients in this group all had excellent results, with complete healing of the skin lesions and also disappearance of arthralgia and fever. See the illustrative cases below. This form of the illness has been graded 2 +.

Patients with subacute systemic lupus are those who have severer exacerbations and remissions of the disease than are found in the chronic form. The skin lesions may vary from being absent to resembling the discoid or acute butterfly type. The patient with discoid lupus who eventually has classic dissemination might be classified in this group. The L.E. test is positive during exacerbations. This form is rated as 3 + in activity in the Table. Three of the five patients in this group, Case 7, M. Sm.; Case 8, J. B., and Case 11, E. J., who had quinacrine dosage increased to toxicity levels and were taking from 300 to 1,000 mg. per day had dramatic improvement. One patient, Case 10, N. G., could not tolerate over 300 mg. per day of quinacrine, and the drug had no effect on her disease. The fifth patient in this category (Case 9, A. K) was given a maximum of only 200 mg. per day during her first course, and the medication was stopped without increasing the dose after 90 days because of a lack of effect. This was prior to our present scheme of increasing the dose to tolerance.

Classic acute systemic lupus has been well described. These patients often have the butterfly eruption, and their disease runs a fulminant course. L.E. cells are usually present. When the patients are treated with cortisone, it is usually necessary to maintain them on the drug for years, because the disease tends not to remit. Whenever the maintenance dose of the hormone is reduced, the illness becomes active again. This form of the disease has been graded 4 +. Eleven of these patients were treated, and the drug was increased to tolerance or clinical effect in 9 patients, the maximum dose utilized being 2,000 mg. per day for as long as 60 days (without toxicity and with marked clinical improvement in Case 12, L. R.). There was no improvement in two patients, who took only 200 to 300 mg. per day for 40 to 60 days. This was also true for a third patient, who tolerated up to 800 mg. per day for 140 days without toxic symptoms. Only two patients in this group had quinacrine alone, without cortisone. One was Case 19, A. C., who had the small doses discussed above, and the other was Case 15, S. O., whose L.E. cells disappeared after six days of treatment with 600 mg. per day. Because of persistent anorexia,

TABLE 1.—*Results of Treatment of Nineteen Patients with Quinacrine*

Case	Diagnosis*	Quinacrine,† Mg./Day	Duration of Treatment, Days	Quinacrine,† Total Gm.	Cortisone,† Mg./Day	Quinacrine Toxicity	Stain	Result of Quinacrine on the Disease
1. A. J.	+	400	46+	18.4+	0	0	+	Complete healing of 8-yr.-old lesions in 3 wk.
2. H. K.	+	300	90+	27.0+	0	0	+	Complete healing of 11-yr.-old skin lesions in 3 wk.
3. C. C.	++	50-100	15	1.1	0	0	0	Rapid healing in 2 wk.; generalized flare-up 60 days after discontinuing treatment; there was a dramatic response to her systemic and local changes with the 2d course of therapy (below)
		600-600	135+	59.7+	0	N & V	0	Findings disappeared 3 days after starting this course of quinacrine; N & V disappeared when dose was reduced to 0.4 gm. per day
4. M. K.	++	200-300	83	18.2	0	0	+	Complete healing in 3 mo. of 18-mo.-old skin lesions
5. C. M.	++	1-400	47	12.3	0	Asthenic feeling	0	Complete healing of 6-yr.-old skin lesions in 30 days and feeling of well-being until last week, when patient discontinued quinacrine; 10 days later mild skin relapse; placed on chloroquine
6. E. P.	++	400-400	56+	8.4	0	N & V	0	Almost complete healing in fourth week of 23-yr.-old lesions; because of N & V, on 200 mg. per day maintenance; marked relief of arthritis in 10 days
7. M. Sm.	+++	300-600	90	35.2	0	N & V	+	5-yr.-old skin lesions healed fully in 4 wk.; arthritis better, but N & V prevented maintenance at this level; when dose was reduced to 300 mg./day, arthralgia recurred; changed to quinine
8. J. B.	+++	200-1,000	123	80.0	75-12.5	Halo about lights; N & V	+	Rash, arthralgia, and strength better; maintained on 0.6 gm. per day due to N & V; changed to chloroquine because of intense yellow stain
9. A. K.	+++	200	90	18.0	100-75	0	0	No effect
10. N. G.	+++	600-300	37	13.2	0	N & V	0	No effect; N & V even on 300 mg./day
11. E. J.	+++	300-300	75+	200+	0	N & V	+	Improvement in arthritis and pleurisy; no rash at this time
12. L. R.	++++	600-2,000	180+	250+	100-0	0	+	Rapid improvement in symptoms; dosage of cortisone could be reduced rapidly without relapse
13. J. F.	++++	200	60	12	100-600	0	+	No effect
14. M. St.	++++	400-1,500	18	16.8	200-600	Dermatitis	+	No effect
15. S. O.	++++	600	16	9.6	0-200	Anorexia, weight loss, gastroenteritis	0	No effect; patient too ill to continue quinacrine alone, because of L. E., and cortisone was started
16. A. S.	++++	600-1,200	44	47.4	100	Mental	+	Rash improvement
17. W. B.	++++	400-2,000	31	46.2	1,750-1,500	Dermatitis	+	No effect
18. G. H.	++++	600-900	42	31.5	125-175	Psychosis	+	No effect
19. A. C.	++++	200	40	8.0	0-100	0	0	No effect
		600-900	60	60.9	25-0	N	0	Arthritis improved; no change in hypertension or renal damage
20. C. R.	++++	600-1,000	53	37.8	200	N & V; dermatitis	+	No effect
21. B. M.	++++	400-800	140	76	75	0	+	No effect
22. M. H.	++++	600-600	50	32.7	25-0	N V & D	+	Rash improved; maintained on 0.3 gm./day

* +, discoid lupus erythematosus; ++, chronic systemic lupus erythematosus; +++, subacute systemic lupus erythematosus; ++++, acute systemic lupus erythematosus (see text for clinical differentiation).

† Doses of quinacrine given are the initial and peak dosages employed; doses of cortisone are those used at the start and end of the period during which quinacrine was administered; + after duration of treatment or dose means patient is still on maintenance therapy at time of writing of paper.

‡ N, nausea; V, vomiting; D, diarrhea.

weight loss, and fever, cortisone was added to her therapeutic regimen. At this time the quinacrine was maintained at the same dosage until 10 days later, when gastroenteritis appeared and the drug was stopped. The patient has continued to do well on cortisone and therefore quinacrine has not been restarted. Another patient in this group had improvement in her rash, but there was no other effect until she developed a mild mental depression and the quinacrine was stopped (Case 16, A. S.). A good result was attained in Case 22, M. H., who had been on cortisone for two and one-half years and had a few small scaly erythematous lesions on her arms and face while still taking 6.25 mg. of cortisone four times a day. Quinacrine was added in a dose of 600 mg. per day, and the rash improved. The cortisone has been discontinued without a relapse. Case 19, A. C., has been given a second course of quinacrine, with improvement in arthritis and ability to completely stop use of cortisone without relapse. There has been no change, however, in his hypertension or renal damage.

The most favorable result appeared in Case 12, L. R., who entered a remission with the combined use of cortisone and quinacrine. The dosage of cortisone could be decreased at a rate much faster than previous experience has shown to be possible in cases of this severity. This may have been a result of the quinacrine. Interestingly enough, this patient had had a psychosis due to lupus cerebral vasculitis, which cleared fully prior to quinacrine therapy, and even with such large doses of quinacrine as 2,000 mg. per day for 60 days her mental state has remained normal. The other five patients with acute systemic lupus had the drug increased to the point of maximum tolerance without any clinical effect.

The clinical results may briefly be summarized as follows, utilizing the grading system outlined above: the less active the disease, the better and more rapid the resultant improvement. Rapid healing occurred in the discoid and chronic systemic forms. Half of the patients with subacute systemic lupus improved, and only one-fourth of those with the acute systemic form improved.

Page [8] has attempted to correlate the production of a yellow stain with the clinical effect. We have not found this correlation. Two patients who had rapid and complete healing of skin lesions had no staining whatsoever. The eight patients with the acute form in whom the drug was most vigorously increased to tolerance had marked yellow staining, but only three showed any improvement.

O'Leary and co-workers [7] state that evidence of dissemination either in the skin or by laboratory examinations is a contraindication to the use of quinacrine because of possible exacerbations. None of these patients have had evidence of aggravation of the disease process by the use of this drug. Since there is such a high incidence of exacerbations in the illness, as well as a 40% incidence of remissions in each attack, an agent will frequently be administered during an exacerbation phase. One should not incriminate the drug because of a few cases.[14] It is safe to try quinacrine in all cases of systemic and discoid lupus; however, the results in the very acute form are poor, and these patients should be given cortisone. Quinacrine can be added if it is desired, to determine whether the steroid dosage can be reduced.

REPORT OF CASES

CASE 4.—*Impressive Effect of Small Doses of Quinacrine in Chronic Systemic Lupus*

M. K., a 28-year-old white woman, was first seen in the dermatology clinic on Dec. 8, 1952, because of a rash on her face for 18 months and arthritis of 13 months' duration. She had been

treated elsewhere with 10 injections of gold, vitamins, liver injections, and iron, without any help. The eruption continued to increase in size.

On examination the temperature was normal. There was a typical discoid type of lesion over the bridge of the nose and covering half the cheek on each side. Several erythematous scaly plaques were noted over the forehead and scalp. Biopsy confirmed the diagnosis.

The only laboratory abnormalities were a white cell count of 4,100, with 36% polymorphonuclear leucocytes, 9% juvenile forms, 46% lymphocytes, 7% monocytes, and 3% eosinophiles. Thymol turbidity was 21 units; cephalin flocculation, 4+. Peripheral blood L.E. cell preparations were negative on three occasions.

The patient was placed on quinacrine, 100 mg. twice daily, on Dec. 15, 1952, and within one week there was less erythema and scaling. At the end of two weeks the rash was improving even more and a slight yellow stain in the skin was noted. At this time, the quinacrine was increased to 100 mg. three times a day. On Jan. 5, 1953, the eruption was greatly improved and the patient noted that her arthralgia was significantly better. The joint pains have not recurred since. On Feb. 9, 1953, the scaling and erythema were completely gone but hyperpigmentation remained, and the dose of quinacrine was reduced to 100 milligrams daily. This was stopped on March 8, 1953. When the patient was last seen, on April 22, 1953, the rash was healed but hyperpigmentation persisted. There was no recurrence of the arthralgia.

Summary.—A 28-year-old woman with evidence of mild systemic involvement had complete healing of her skin lesions and disappearance of arthralgia and weakness within six weeks. There was no recurrence after the medication was stopped for five weeks.

CASE 3.—*Rapid Healing Which May Occur in Cases of Chronic Systemic Lupus Erythematosus*

C. C., an 11-year-old Negro girl, was first seen at the hospital in 1949, complaining of arthralgia. She had been in good health until five years of age, when after exposure to sunlight an erythematous eruption in the butterfly area developed, which persisted for several weeks and then disappeared. This was diagnosed as lupus erythematosus at the time. The patient had numerous recurrences of this rash without systemic symptoms until March, 1949, when generalized arthralgia appeared, with fever (temperature of 100 F.), generalized adenopathy, precordial pain, a systolic heart murmur at the apex, and electrocardiographic changes suggestive of pericarditis. This illness lasted four months, and there was a spontaneous remission. Several similar episodes occurred during the next four years.

A skin biopsy, taken in July, 1950, during a cutaneous exacerbation, was interpreted as being consistent with discoid lupus erythematosus.

Her relapses were associated with increased physical activity. Laboratory studies during exacerbations were all normal, aside from a sedimentation rate of 21 mm. in an hour (Wintrobe); nine L.E. tests were negative, including a bone marrow and a cantharides blister test. Since September, 1952, she had a persistent erythematous papule 1 cm. in diameter on the bridge of her nose.

During an exacerbation, on Feb. 26, 1953, she was placed on quinacrine, 25 mg. twice daily. Ten days later there was no change, and the dosage was increased to 50 mg. twice daily. Within one week the lesions faded and quinacrine was stopped. Two weeks later the lesions were completely gone. There was no evidence of skin staining. The patient felt generally better during quinacrine treatment and did not have occasional bouts of fever while on the drug.

Two months after the drug was discontinued, in May, 1953, there was another flare-up of joint pain, temperature to 101 F., and the rash. The white blood cell count was 4,300 with a normal differential count. The patient was placed on quinacrine, 600 mg. per day, and within three days the rash had almost completely faded, joint pains had cleared, and she was afebrile, but nausea and vomiting appeared from the quinacrine. The dosage reduced to 400 mg. per day was well tolerated, and five days later the eruptions had almost completely disappeared and the patient felt well. The white cell count had risen to 10,600 at this time. Twelve days after quinacrine therapy was started the rash had completely disappeared. The patient was maintained on 400 mg. per day for over 85 days. At that time a gastroenteritis appeared, which stopped when the maintenance dose of quinacrine was reduced to 200 mg. per day. When the

patient was last seen, on Nov. 4, 1953, the rash remained absent, despite a great deal of physical activity, which used to cause exacerbations of the eruption with fever and arthralgia. There was no yellow stain or evidence of quinacrine toxicity.

Summary.—An 11-year-old Negro girl with chronic systemic lupus erythematosus, in addition to an acute erythematous butterfly eruption, had fever and arthralgia. She responded well to quinacrine on two occasions; the first time the symptoms and findings disappeared in 17 days on a maximum dose of 100 mg. per day. The drug was stopped, and two months later she had a severer relapse, which was controlled by 600 mg. of quinacrine per day. Within three days the patient was afebrile and the rash had greatly faded. She has been maintained on from 200 to 400 mg. per day for the past 135 days without evidence of skin-staining or toxicity.

CASE 7.—*Subacute Systemic Lupus Which Responded Well to Therapy*

M. Sm., a 36-year-old Negro woman, was admitted to the Los Angeles County General Hospital on Feb. 9, 1953, complaining of a facial rash of one year's duration. The patient had been in good health until four years prior to admission, when she developed vague complaints of headaches, abdominal pain, and weakness. In October, 1948, scaly atrophic lesions appeared on the buttocks, and these gradually spread. Her symptoms progressed, and she first consulted a physician in October, 1951, who found her hemoglobin to be 10.1 gm.

The following month, areas of hyperpigmentation appeared on her cheeks, and during the spring of 1952 her legs became scaly and patchy areas of hyperpigmentation were noted on them. In July, 1952, the patient was seen at the dermatology clinic, where there were found circinate bordered plaques with follicular plugging and atrophy on the legs. Biopsy was consistent with lupus erythematosus. Similar areas had been present on the cheeks for four months.

In November, 1952, arthralgia appeared in the arms, legs, wrists, and fingers. Several transitory tender nodular swellings were noted along the course of the tendon sheaths of the left hand and forearm. Because of the persistence of these symptoms, the patient was admitted on Feb. 9, 1953. Physical examination showed a well-developed well-nourished 36-year-old Negro woman in no distress, with skin lesions as noted above. There was slight spindle-shaped doughy swelling of the proximal interphalangeal joints of both hands. Her temperature during hospitalization varied from 99 to 100 F.

The only abnormalities in the laboratory studies were a hemoglobin level of 10.0 gm., and white cell count of 5,450, with a normal differential count. Sedimentation rate was 36 mm. in an hour (Wintrobe). Three peripheral blood and one bone marrow L. E. preparations were negative. Lumbar puncture revealed 1,300 lymphocytes. Protein level was 25 mg. per 100 cc.

The arthralgia and fever persisted. On April 7, 1953, the L. E. preparation was 4+. On April 22, 1953, quinacrine therapy was begun in a dosage of 400 mg. per day. On April 24, 1953, the L. E. preparation was 1+. On April 25, 1953, the dose was increased to 0.6 gm. per day, and two days later the L. E. preparation was negative. After 11 days on this amount of drug, the skin became yellow and gastroenteritis appeared. Quinacrine dosage was reduced to 300 mg. per day, and these symptoms cleared. At this point the joint pains and fever were gone. However, the L.E. preparation again became 1+ and has remained so. After 25 days of atabrine therapy, the skin was entirely healed. Although the patient's symptoms were under good control, there was no rise in her hemoglobin level. Therefore, an attempt was made to increase quinacrine dosage further, but several weeks after the dose was raised to 600 mg. per day gastritis recurred, and it was reduced again to 300 mg. per day. On July 18, after the patient had been taking 300 mg. per day for one month, the nausea and vomiting recurred. At this time the L. E. preparation was still 1+. Several weeks after quinacrine was stopped the arthralgia recurred, and the patient was placed on quinine sulfate, 1.2 gm. per day. Within seven days there was improvement. On quinacrine therapy, her hemoglobin level rose slightly, from 10.0 to 11.4 gm., and the white cell count rose from 4,300 to 6,350.

Summary.—A 36-year-old Negro woman had subacute systemic lupus erythematosus. L.E. cells were discovered after she had been ill for four years. Fourteen days after starting quinacrine her arthralgia and fever were gone and the rash was

beginning to heal. L.E. cells were abundant prior to therapy, and within two days they almost completely disappeared.

The skin lesions were completely healed after 25 days of treatment. Quinacrine was stopped after 90 days because of nausea and vomiting. Within several weeks that patient's joint pains recurred. She was then given quinine sulfate, and again her symptoms rapidly disappeared.

TOXICITY OF QUINACRINE IN LARGE DOSES

Quinacrine was increased to the point at which clinical improvement occurred or at which there was toxicity which precluded further increase in the dosage in 20 patients. If there was nausea and vomiting or gastroenteritis, the dose was reduced temporarily and then raised again, if possible. With the appearance of a psychosis or dermatitis, the drug was stopped completely. Toxic symptoms were noted in 16 patients given doses of 100 mg. per day or more. The commonest symptoms were nausea and vomiting, in 10 patients given doses of as little as 300 mg. per day. Some patients can tolerate as much as 2,000 mg. per day for months, without toxicity. Because of the fact that the blood level of quinacrine is cumulative, gradually rising on a stable dose to a peak after four to six weeks, toxicity may not appear for weeks and may persist from days to weeks after the drug is stopped.[15]

TABLE 2.—*Quinacrine Toxicity in Twenty-Two Cases*

Symptoms	Cases, No.
Yellow stain	15
Nausea and vomiting	10
Dermatitis	3
Halos	1
Mental depression	1
Psychosis	1

Colored halos around lights were noted by one patient. A dermatitis characterized by dry papular scaly erythematous lesions on the thighs was seen in three patients after 18 to 31 days of therapy with maximum daily dosages of 1,000 to 2,000 mg. per day. All these patients had active lupus and were on maintenance cortisone. It is possible, but unlikely, that this eruption could have been due to the underlying disease. In all three, dosage of cortisone was raised and the quinacrine was stopped, and within several weeks the rash cleared. There was no effect of the quinacrine on the underlying disease. One patient, after 44 days of therapy (Case 16, A. S.), became slightly depressed mentally, and, although her lupus rash had improved under treatment, the drug was stopped. Case 18, G.H., after 42 days of quinacrine with doses as high as 900 mg. per day, became markedly psychotic and was hospitalized. She was disoriented as to time and was screaming out names and numbers. Quinacrine was stopped, and cortisone and potassium were maintained at her usual dose. Fluids were forced, and after five days the psychosis cleared completely. Quinacrine has not been restarted. No patient showed evidence of any toxic effect on the peripheral blood picture. Table 2 summarizes the toxic symptoms.

EFFECT OF QUINACRINE ON L. E. PHENOMENON

As mentioned above, I have demonstrated, in preliminary studies,[12] that in vitro concentrations of over 20 mg. per 100 cc. of quinacrine will completely inhibit the L.E. phenomenon. Pilot studies with other antimalarials reveal that much higher

concentrations are required to do the same thing. The dose of quinine, for example, must be over 40 mg. per 100 cc., and that of chloroquine, over 80 mg. per 100 cc.

Quinacrine blood levels were determined while the dose was gradually increased to the point of maximum toleration. The highest level obtained was 0.096 mg. per 100 cc., which is about 1/100 of the theoretically desired blood level, if it is necessary to have the same plasma level in the patient as in the test tube to inhibit the L.E. phenomenon. However, it is important to note that the levels of quinacrine in the white cells themselves are 100 to 300 times the plasma level, and so with these large doses the leucocytes and certain organs of the body, as liver, spleen, and lung, will have tissue levels within the potent range.[16] The quinacrine concentration in these latter tissues may be as high as 20,000 times the plasma level.

We have had the opportunity to study the effect of large doses of quinacrine on the L.E. phenomenon in three patients given that drug alone and in a fourth, given quinacrine and cortisone. The maximum plasma level attained in the first patient was 0.038 mg. per 100 cc. The L.E. test decreased from 4 + to 1 + in one week. The clinical improvement was rapid, however (Case 7, M. Sm., above). In the second patient the L.E. test reverted from 4 + to negative in one week, but at this time, because of a lack of clinical improvement in this critically ill patient, cortisone was added to the therapy. Quinacrine continued in a dose of 0.6 gm. per day for another 10 days, but acute gastroenteritis developed, and it was stopped. The patient continued to do well on cortisone maintenance dosage, and quinacrine has not been restarted (Case 15, S. O.). In the third patient (Case 11, E. J.) the L.E. preparation reverted from 1 + to negative after two weeks of quinacrine therapy. With cortisone alone it requires four to six weeks of treatment for the L.E. test to become negative.[11] In a fourth patient, with very active systemic lupus erythematosus, on maintenance cortisone therapy, the L.E. cells disappeared after 10 days of quinacrine treatment (Case 14, M. St.). However, nine days later an erythematous dermatitis appeared on the thighs, which may have been due to the drug but also could have been due to the relapse of the underlying illness. The quinacrine was stopped, and the dose of cortisone was raised. One month later the rash had completely disappeared.

COMMENT

The discovery that quinacrine is of value in the treatment of discoid lupus and the finding that it aids the chronic form, the subacute systemic form, and, occasionally, even the acute stage of the disease is a significant advance in the treatment of this ailment. The effect of the drug on the discoid lesions is apparently a relatively specific one, because of the rapidity with which it heals even the very long-standing lesions in several weeks. The improvement in the arthralgia and fever may not be as specific an effect, for 8-aminoquinolines have been demonstrated to help rheumatoid arthritis.§ Atabrine, in vitro, inhibits the L.E. phenomenon in smaller amounts than quinine, quinidine, primaquine, daraprim, chloroquine, and pamaquine. Hence quinacrine may act upon the fundamental enzymatic dysfunction that is probably the cause of the disease. Haserick has shown that cortisone, corticotropin, penicillin, nitrogen mustard, estradiol, progesterone, chronic discoid L. E. plasma, and testosterone do not inhibit the L.E. phenomena in vitro.[20] Another mechanism by which quinacrine may act is as an

§ References 17-19.

ultraviolet light filter. Experimental studies have shown that subjects who take quinacrine can absorb more ultraviolet light without developing erythema. The drug is known to be of value in sunlight-sensitivity eruptions.

Nelson and co-workers [15] point out that the plasma concentration of quinacrine reaches 50% of its equilibrium level on a stable dose by the end of the first week and that by the fourth week 94% of that level is attained. The maximum clinical improvement in patients with discoid lupus maintained on stable doses of quinacrine began usually about the fourth week.[8] If one doubles the maintenance dose for the first week, the equilibrium level is reached at the end of one week instead of four. In Case 3, C. C., the rash was greatly improved and the arthralgia and fever (temperature of 100 F.) had completely disappeared after three days' treatment with 600 mg. of quinacrine per day, whereas with smaller doses 17 days were required for improvement to occur. Hence, in order to obtain a more rapid result in treating the discoid form, it would be better to start the patient on a dose of about 300 mg. per day for a week, which usually is tolerated well, and then reduce it if necessary the following week in the milder cases or raise the dose in the severer forms. This means that a higher blood level of quinacrine is more readily attained, and apparently the clinical effects follow the blood level.

Twelve patients of 20 who were vigorously treated showed improvement, which began in as little as three days. Several patients who had had lesions 2 to 3 cm. in diameter for as long as 10 years had complete healing in three weeks, compared with results in other series, which report months for healing to occur. This can probably be attributed to the higher dosages used in this study.

SUMMARY

Twenty patients with systemic lupus erythematosus and 2 patients with the discoid form have been treated with quinacrine (Atabrine). In 20 cases an attempt was made to increase the drug to the point of clinical improvement or maximum tolerance. Doses as large as 2,000 mg. per day for 60 days have been used. If nausea or vomiting appeared, the dose was temporarily decreased; however, if a psychosis or dermatitis appeared the drug was stopped.

The results may be correlated with the clinical classification. The discoid form is the one in which patients have lesions limited mainly to the face, with no clinical or laboratory evidence of dissemination. The two patients in this group had complete healing. Chronic systemic lupus erythematosus is that form in which there are discoid lesions on the face and, usually, on the body as well, with occasional flare-ups of systemic involvement, such as arthralgia, fever, and abnormal liver-function tests, but negative L.E. tests. In the four patients in this group there was healing of the skin lesions as well as disappearance of the systemic symptoms. Subacute systemic lupus is a slightly more virulent form, with remissions and exacerbations, in which L.E. cells are usually found. Of the five patients with this type of the disease, three were greatly improved. Classic acute systemic lupus erythematosus is that in which the patients have the typical fulminating clinical syndrome, without remissions after a year or more of treatment with cortisone. Of 11 patients with this form, only 3 showed improvement, despite vigorous treatment. In general, the less active the disease was, the more rapid and better was the resultant improvement.

Only one serious toxic reaction occurred, namely, a psychosis, which disappeared after one week's hospitalization. Three patients developed a dermatitis that disappeared on cessation of the drug.

In view of the cumulative property of quinacrine and the fact that clinical improvement tends to follow the production of a maximum blood level, it is suggested that quinacrine be started at a level of 300 mg. per day for the first week and, if one is treating the discoid patient, that the dose be reduced or, if it is the more virulent form of the disease, that the dosage be raised gradually to the point of improvement or toxicity. It is not necessary to produce a yellow stain in order to have clinical improvement.

Quinacrine is of definite benefit in the treatment of discoid, chronic systemic, and subacute systemic lupus. It is the first great advance in the therapy of this disease since the advent of cortisone and is well worth a trial in all patients with these forms of the disease. Studies with other antimalarials are under way, and perhaps these will enable us better to treat the acute form of lupus erythematosus.

ADDENDUM

Since this paper was written, an additional 20 patients have been treated with quinacrine, utilizing the same methods of therapy. They were treated in conjunction with Dr. Stewart Martel, of the dermatology department. The results have been similar to those reported in the body of the paper. Three patients with discoid lupus, four cases of chronic disseminated lupus, and six patients with the subacute systemic form were treated, with good to excellent results. Seven patients with the acute disseminated form received the drug. Only three were greatly benefited. The other four either were not helped or were made toxic.

Seventeen persons, including some who could not tolerate quinacrine or who developed toxic symptoms after long-term maintenance on it, have had a course of chloroquine (Aralen) in doses up to 2 gm. a day. A similar attempt was made to increase the drug to maximum tolerance or benefit. Two of three patients with chronic disseminated lupus were helped. The third could not tolerate the drug. Four of six cases of subacute disseminated lupus were greatly benefited. In the other two no effect was demonstrated. Eight patients with acute lupus were treated, and three improved considerably. The other five either were not helped or became toxic from the drug. One patient on 0.75 gm. per day developed a transitory leucopenia after six weeks of treatment.

Seven patients received quinine in doses as high as 2.8 gm. a day. Only one of three patients with the subacute form was helped. Two of four patients with the acute type were greatly benefited, and in one cortisone could be stopped for the first time in more than two years. The other two patients were not helped.

Eight persons have been given combinations of two antimalarials, with each drug increased to maximum tolerance or benefit. The results seem favorable, but it is too early to judge.

I feel that it is worthwhile trying the antimalarials in all cases and forms of lupus erythematosus. Although the results in the acute and subacute disseminated form with this therapy are not as good as in the milder stages of the disease, it is particularly valuable because a remission may be initiated during which the patient can stop cortisone or the maintenance dose of the drug can be reduced, thereby reversing

the catabolic effects of long-term adrenal steroid maintenance therapy. Even if a relapse should occur after several months of antimalarial therapy, at least the patient has had the opportunity to heal his osteoporosis and peptic ulceration, reverse his negative nitrogen balance, and clear up other changes due to adrenal steroid therapy. Then he is in a better condition for a second course of steroids if they should become necessary.

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Progress in Internal Medicine

DIALYSIS IN TREATMENT OF UREMIA

Artificial Kidney and Peritoneal Lavage

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BETTER understanding of water and electrolyte balance and new concepts of treatment have made conservative management of uremia more effective. The majority of patients with acute urinary suppression now recover, but their management remains difficult, and the results are not always satisfactory; death still takes a toll.

Hemodialysis should not be considered a competitor but, rather, a valuable adjunct to the medical management of acute and chronic uremia. This report reviews the principles, techniques, indications, and dangers of various dialyzing procedures.

I. EVALUATION OF ARTIFICIAL KIDNEY

Statistics concerning increased survival with the use of an artificial kidney are scarce. Hollingsworth Smith reported at a committee meeting of the National Research Council, in Washington, March 18, 1953, that the mortality rate of severely wounded anuric soldiers in Korea was reduced from approximately 90% to 60% when an artificial kidney was employed behind the front lines. Such reports are encouraging, but, owing to other concurrent changes in treatment, they may not be statistically significant.

The survival rates of patients treated with the artificial kidney by Merrill's group, in Boston, or by Alwall, in Lund (Sweden), or by ourselves are not comparable to the survival rates in hospitals without an artificial kidney, since artificial kidneys attract unusually severe or complicated cases from a wide environment, and it is usually the complications or the underlying disease which determines the ultimate survival.

Stock[1] reviewed 52 cases of acute urinary suppression not treated with dialysis; 14 patients of his own, 11 treated by Bull, Joekes, and Lowe,[2] and 27 treated by Muirhead, Vanatta, and Grollman.[3] In the 52 cases there were 11 deaths. Stock attributed only one death to accumulation of retention products. Thus, he concluded that there is no place for the artificial kidney in the treatment of uremia. But review of this series reveals that 9 of the 11 patients had complications, such as dehiscence of an abdominal wound, pulmonary edema, bronchopneumonia, or cerebral hemorrhage, that are prone to occur in severe uremia and that might have been prevented or relieved by timely use of dialysis.

The best indication of the usefulness of the artificial kidney comes from careful evaluation of its use in individual patients. The following example is illustrative:

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A review covering the same material has been prepared for the Veterans Administration Technical Bulletin TB-97.

In 1945 we treated a 67-year-old woman who had cholecystitis, hepatorenal syndrome, and anuria of 7 to 10 days' duration. The blood urea was 400 mg. per 100 ml., and the serum potassium was 11.5 mEq. per liter. She was almost comatose. After treatment with the artificial kidney, the blood urea was reduced to 120 mg. and the serum potassium to 5.8 mEq. per liter. The next day the patient was completely clear of mind and made reasonable plans for her future. The clinical improvement was probably due to the removal of retention products and the correction of electrolyte balance. During the following days diuresis began and slowly increased. She made a complete recovery.[4*]

Patients who seemed moribund have been revived by treatment with artificial kidneys or peritoneal lavage.† But while there is no doubt that life has been prolonged in many instances, ultimate recovery is not always obtained, owing to the underlying disease or to complications that we have not yet learned to overcome. To illustrate this with another example, one of our patients, a woman 37 years old, died of pneumonia 74 days after the onset of an almost complete symmetrical renal cortex necrosis. She had been given the "Borst forced high-calorie diet" and had been treated twice with the artificial kidney and twice with peritoneal lavage.

Experimental work confirms these observations. Dogs made anuric by a usually lethal dose of 5 mg. anhydrous uranyl nitrate subcutaneously were saved by repeated treatment with an artificial kidney.[7] The artificial kidney has prolonged life in dogs for as long as 25 days after bilateral nephrectomy[8]; with peritoneal lavage, it has been possible to maintain life in bilaterally nephrectomized dogs for 40 days,[8] 69 days,[9] and 110 days.[10]

Vanatta, Muirhead, and Grollman have logically concluded that the clinical picture of uremia is due to accumulation of retention products, since it is relieved by their removal by dialysis.[11] The results of dialysis also indicate that excretion of retention products and regulation of electrolytes are of primary importance for maintenance of life and that other metabolic functions, such as "two consecutive beta oxidations of fatty acids" [12] and formation of ammonia, are of lesser importance.

One metabolic function of the kidney, which is poorly understood and defined, probably cannot be replaced by the dialyzing method. It is the function that serves to maintain normal blood pressure. The hypertension and cardiovascular disease that follow bilateral nephrectomy[8] are supposedly due to lack of this kidney function.[13]

II. GENERAL PRINCIPLES OF TREATMENT OF UREMIA

It would be unfortunate if the medical management of uremia were neglected due to overemphasis on the use of the artificial kidney. The over-all management of uremia may be summarized as follows:

A. Restriction of fluid and electrolyte intake either orally or by other means during the period of anuria. Seven hundred and fifty milliliters of fluid per day compensates for insensible water loss; more may be necessary if there is weight loss that is due to excessive transpiration, vomiting, or diarrhea. Sodium salts, as a rule, should not be given to patients during the period of anuria, as sodium is not excreted. Sometimes NaCl may be replaced when it has been lost in great quantities, for example, by vomiting, but this is rarely necessary. Small doses of

* For reports of similar cases see References 5 and 6.

† References 4 and 5.

$NaHCO_3$ are sometimes indicated in severe acidosis. In emergencies, hypertonic NaCl may be used to counteract the electrocardiographic changes of potassium intoxication. The administration of hypertonic glucose solution or the use of potassium-binding resins is to be preferred if there is no immediate danger from hyperpotassemia.

B. Suppression of protein catabolism by forced administration of a high-calorie regimen (Borst principle).‡ There is little doubt about its usefulness in the treatment of chronic uremia. In acute uremia opinions differ. I feel it should be tried and used as far as practical.

C. Prevention or treatment of infection with antibiotics. Since in renal failure antibiotics are poorly excreted or not at all, dosages should be low, especially of potentially dangerous drugs, like streptomycin (vestibular damage).

D. Avoidance of elective surgery, excessive transfusion, and other procedures that may increase protein catabolism and the production of retention products.

E. Removal of retention products and correction of body chemistry by dialysis (artificial kidney, peritoneal lavage, and intestinal lavage).

III. PRINCIPLE OF ARTIFICIAL KIDNEY

The principle of most artificial kidneys is the same today as it was in 1912, when the procedure was introduced by Abel, Rowntree, and Turner.[16] Clotting of blood in the apparatus is prevented by heparin. Blood is either withdrawn with a pump from a large vein or taken from an artery and guided through a system of dialyzing membranes (tubes or sheets) with blood on one side of the membrane and the rinsing fluid on the other side. Dialysis, which means purification by diffusion through a semipermeable membrane, then occurs (Graham, 1861). Molecules of small size pass through the membrane; large molecules and blood cells do not. Fortunately, all known retention products, such as urea, uric acid, creatinine, and phenols, are able to pass through the membrane. Their relative rates of dialysis have been determined by Wolf and associates.[17] Most bacterial toxins will not dialyze.

If the rinsing fluid is large in volume or is continuously changed, the diffusion gradient is sufficiently great to prevent excessive back diffusion of retention products. In this respect the artificial kidney has a definite advantage over the human kidneys, where reabsorption takes place in the tubules. Water, salts, and glucose pass through the semipermeable membrane in both directions as salts and glucose are added to the rinsing fluid. Electrolyte equilibrium between blood and rinsing fluid occurs if dialysis is continued for a sufficient period of time. The plasma electrolyte content can be changed at will by varying the composition of the rinsing fluid.

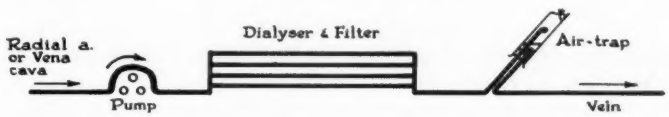
The dual function of the artificial kidney in adding or in withdrawing of specific blood constituents is illustrated in the treatment of acidosis. First, an excess of anions is corrected as acid retention products pass through the membrane into the rinsing fluid. Second, a deficit in buffer base is corrected as Na^+ diffuses into the blood until equilibrium with the rinsing fluid is obtained. The end-result is correction of the acidosis and establishment of normal electrolyte content of the blood.

‡ References 14 and 15.

The water movement across the membrane is governed by hydrostatic forces; by osmotic forces of urea, salts, glucose, and other substances on both sides of the membrane, and by colloid osmotic pressure of the plasma proteins. Blood that has passed once through the dialyzing system of an efficient artificial kidney is almost cleared of urea when it reaches the outflow end of the apparatus.[18] It is then returned to a vein of the patient, and during the next circulation through the body the blood is reloaded with retention products. Thus, the process of clearing the patient's blood is slow. With most artificial kidneys now in use there is a continuous flow of 12 liters of blood per hour through the apparatus. The reduction of blood urea from high to nearly normal levels requires from 5 to 12 hours of treatment and depends greatly on the weight of the patient. Large amounts of urea and other retention products can be removed. We once removed 263 gm. of urea in one dialysis. Dialysis may be repeated, if necessary, after four or five days.

IV. TYPES OF ARTIFICIAL KIDNEYS

A. Artificial Kidneys Using Dialysis Only.—These include Kolff's rotating artificial kidney, which will be discussed in detail later, and Guarino's [19] type, which is new and now in the process of being tested. Both types use Cellophane tubing.



DIALYSIS & FILTRATION

Fig. 1.—Diagram of filtering and dialyzing type of artificial kidney. The pump to the left forces the blood through a system of dialyzing membranes. Rinsing fluid (not shown) circulates on the outside of the membranes. As the blood is under pressure, dialysis and filtration take place.

B. Artificial Kidneys Wherein Blood is Pressed Through a Dialyzing System.—Filtration as well as dialysis occurs, depending on the pressure gradient between blood and rinsing fluid in this type of apparatus. Figure 1 indicates the manner in which blood is passed through the system of Cellophane sheets or Cellophane tubes either by arterial pressure or by a pump. The rinsing fluid flows on the outside of the Cellophane membranes, and the membranes are supported by screens or plastic or rubber ridges; otherwise the blood volume would be very inconstant. Some artificial kidneys § are more or less monumental relics of the preclinical period. The kidneys made by Alwall,|| Murray,¶ Rosenak and Saltzman,[32] Bodo von Garrelts,# and MacNeill [34] and Kolff's stationary type * use Cellophane tubing compressed either between screens [32] or grids † or tubes of small diameter [31] to keep the blood volume in the appartus as low as possible. Some ‡ use Cellophane sheets sandwiched

§ References 16 and 20-22.

|| References 23-29.

¶ References 30 and 31.

Cited by Kolff.[33]

* References 33 and 35.

† References 23-29, 33, and 34.

‡ References 7, 36, and 37.

between grooved plates. In the artificial kidney of Skeggs, Leonards, and Heisler, Model 2,[7] blood flows between pairs of Cellophane sheets held in place by grooved rubber plates. The rinsing fluid flows through the grooves of the rubber plates. This apparatus can be used as an ultrafilter when positive pressure is applied against the blood or suction is applied to the rinsing fluid.

C. Artificial Kidneys Using Filtration Only.—Malinow and Korzon [38] built an apparatus by which large amounts of ultrafiltrate can be removed; in terms of urea clearance it is inferior to the dialyzing machines.

D. Artificial Kidneys Using Resins.—Muirhead and Reid [39] have demonstrated their possible use, and de Marchi and Brönnimann [40] had encouraging clinical experience with a resin type of artificial kidney. Careful conditioning of the resin bed is necessary to prevent undue absorption or elution of electrolytes. This approach is even more promising as new and better resins are being developed.

E. Efficiency of Various Artificial Kidneys.—The efficiency of artificial kidneys is usually expressed in terms of urea clearance. The clearance of an artificial kidney represents the virtual volume of blood cleared of a given solute in a measured time interval. Assuming that the bath-water in the beginning is fresh, the value for clearance is obtained as follows:

$$\frac{\text{concentration in bath} \times \text{volume of bath}}{\text{concentration in blood}}$$

Again, when the bath water is fresh, clearance is equal to "dialysance," a term preferred by Wolf and his associates.[17]

The urea clearance of the rotating kidney at a flow rate of 200 ml. per minute is 170 ml. per minute.[18] The urea clearance of the Skeggs, Leonards, and Heisler kidney is 125 ml. per minute at the same flow rate. The clearance of other artificial kidneys is less.[41] High clearances of urea are desirable, because the clearance for most other solutes is much less. With urea clearance as a basis of comparison, clearance of uric acid is only 45%; clearances of inorganic phosphate and sulfate are 32% each, and the clearance of phenol red is only 11%.[17]

F. Rotating Type of Artificial Kidney.—In Figure 2 it is shown that blood comes from the radial artery and passes first through a flow meter § and then through a rotation coupling and into the Cellophane tubing,‖ which is spirally wrapped around a rotating drum. While the drum rotates, at 25 revolutions per minute, the blood seeks the lowest level in the Cellophane tubing and consequently runs through the spiral from left to right. Thus the tubing on the bottom half of the drum is only partly filled and a film of blood remains in the collapsed Cellophane tubing on the upper half of the drum. There cannot be much difference in hydrostatic pressure inside and outside the Cellophane tubing, and there is no filtration. At the end of the Cellophane tubing, blood enters a plastic tube and leaves the artificial kidney through another rotating coupling in the hollow axle of the drum. With the assistance of a pump it is then returned to a vein after passing through a clot-and-bubble catcher. Flow of blood is continuous and approximates 200 cc. per minute. The lower half of the rotating drum rests in a tank containing 100

§ Flow Rater B-2-A-127 with ¼ in. (0.6 cm.) diameter glass ball; Fisher and Porter, Hatboro, Pa.

‖ Cellophane tubing, 20/32 or 23/32 in. inflated diameter; The Visking Corporation, 6733 West 65th St., Chicago.

liters of rinsing fluid. However, tubing on the upper part of the drum remains wet, and so dialysis occurs there too, provided the level of fluid in the bath is high enough.¶

V. TECHNIQUE OF EXTRACORPOREAL DIALYSIS

A. Preparation of Apparatus.—It is not the purpose of this report to give detailed instructions for the assembling of artificial kidneys,# but some points of general interest will be discussed.

The artificial kidney team should consist of a technician to operate the apparatus; a technician to perform laboratory determinations, in particular the clotting times; a nurse to insure the patient's comfort, and a physician to supervise the team and perform such procedures as cannulizations.

New Cellophane tubing or membranes are used for each patient. It is possible that Cellophane contains substances that cause chills, fall in blood pressure, and other undesirable reactions. Some have advocated chemical treatment [11]; others, prolonged boiling to remove these substances.[43] We boil the Cellophane tubing for

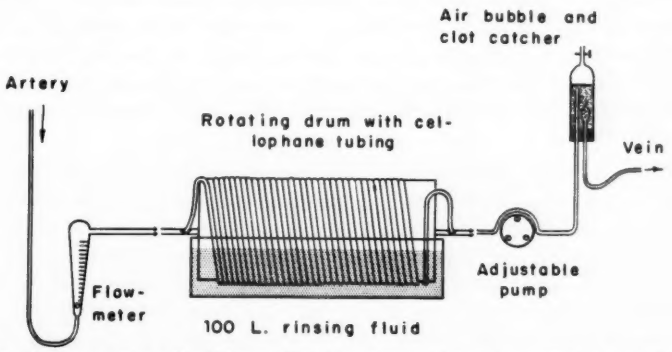


Fig. 2.—Diagram of rotating kidney. The blood comes from the radial artery; the rate of flow is measured by a flow rater and controlled with a screw clamp. The blood passes through the hollow axle of the drum and enters the Cellophane tube. Once in the Cellophane tubing, it moves by gravity when the drum rotates. The Cellophane tube is not filled like a sausage; just a thin film of blood moves through the Cellophane. A pump returns the blood to a vein of the patient.

two hours on a wooden reel that allows the boiling water to reach every part of the tubing. It may be stated, however, that in emergencies (and in numerous experiments on dogs) we have used Cellophane tubing without boiling and that we have observed no ill effects (see Addendum).

All glass parts, except the flow meter, are coated with silicone * to make the surface water-repellent. This and the use of dispensable polyvinyl chloride tubing (Tygon) instead of rubber tubing help to minimize the required amount of heparin.

After assembling the artificial kidney we fill it with benzalkonium (Zephiran) for sterilization. It remains filled with benzalkonium and ready for several days.

¶ Variants of Kolff's rotating type of artificial kidney are produced by Allis-Chalmers, Milwaukee, and Edward A. Olsen, Main St., Ashland, Mass. For detailed plans of construction, see Reference 4.

References 4 and 42.

* Dow Corning Panglaze 2% in carbon tetrachloride, bake 20 minutes at 400 C.; Dow Corning Corporation, Midland, Mich.

The artificial kidney of Skeggs, Leonards, and Heisler can be sterilized with steam. Others prefer to keep most parts which come in contact with blood in a kit that can be sterilized in an autoclave [42]; the other few items are sterilized by benzalkonium.

We rinse the artificial kidney with 20 liters of sterile water and a few liters of saline solution to remove the benzalkonium; it is checked for leaks and then primed with 500 ml. of fresh matched bank blood to which heparin has been added.

While the kidney is being prepared, the blood vessels to be cannulated are exposed. We prefer to use the radial artery rather than cannulization of the vena cava inferior via the saphenous vein. The cut-down wound for the radial artery need not exceed 1.5 cm. The radial artery has been ligated in hundreds of cases without trouble. Collateral circulation is checked beforehand by compressing the artery and feeling a pulse in the distal end; this, however, is not always possible. The same radial artery may be exposed 3 cm. higher and used for the next treatment. With a proper cannula † flow of blood from the radial artery usually exceeds 200 ml. per minute; flow is adjusted with a screw clamp and measured with a flow rater. The blood is reintroduced into a cannulated peripheral vein (the cubital veins are always saved). At the end of treatment one might be tempted to reinfuse the blood present in the apparatus into the patient. However, the introduction of 500 to 700 ml. of blood into these patients at the end of the dialysis entails the risk of overloading the circulation, which would be followed by pulmonary edema a few hours later.

B. Heparin Dose.—Initially, 80 to 120 mg. (8,000 to 12,000 units) of heparin are given to the patient and 40 mg. are added to the 500 cc. of citrated bank blood used to prime the artificial kidney. The arterial and venous cannulae are filled with saline solution and 5 mg. of heparin each. During dialysis, we check the clotting time every half hour, although others, with large experience, do not. When it becomes shorter than 20 minutes during the first three hours of dialysis, we give more heparin into the tube leading from the radial artery to the artificial kidney. The aim is to maintain clotting time at approximately 20 minutes with hourly injections of 5, 10, or 20 mg. of heparin. During the last hours of the dialysis, a clotting time of 12 minutes is permitted. The total amount of heparin administered is approximately 200 mg. (20,000 units), but it may be less if there is particular danger from hemorrhage. The clot catcher in the artificial kidney is an essential safeguard. We have a replacement ready in case the first one gets clogged.

C. Rinsing Fluid.—Composition of typical rinsing fluid is presented in the Table. Lactic acid is added to bring the pH to 7.4, where it is maintained by blowing a constant stream of 10% CO_2 in oxygen through the rinsing fluid or under the hood of the artificial kidney. If the pH rises, calcium in the rinsing fluid is gradually precipitated as calcium carbonate; in this case 1 or 2 gm. of calcium gluconate should be injected intravenously to prevent calcium depletion.

It will be noted in the Table that the sodium concentration in the rinsing fluid is lower than in normal plasma, since the plasma sodium of patients with uremia is often low. Correction to a normal level may cause the development of hypertension, pulmonary edema, or cardiac failure. The electrolyte pattern should be determined before treatment is begun and the rinsing fluid adjusted accordingly; sodium con-

† References 4 and 42.

centration of the rinsing fluid is made to fall midway between normal and the respective patient's blood sodium. If the serum potassium is high, potassium content of the rinsing fluid is lowered (0 to 2.5 mEq. per liter, or 20 mg. per 100 cc.).

Wolf ‡ has calculated that urea removal by the rotating type of artificial kidney may be augmented 16% if the 100-liter bath of rinsing fluid is changed halfway through the dialysis.

Glucose is added to the rinsing fluid for the following reasons:

1. To compensate for the osmotic pressure of urea and the colloid-osmotic pressure of the plasma proteins. At a certain difference between glucose concentration in the rinsing fluid and the average concentration of glucose in the blood, water transport in both directions through the Cellophane is the same. Wolf and his associates [17] determined in two patients that water balance occurred when the difference between blood and bath glucose was 360 mg. per 100 ml. in one and 660 mg. per 100 ml. in the other. Glucose concentration of 750 mg. per 100 ml. (0.75%)

Composition of Rinsing Fluid

	Mg./100 Ml.		Na^+	K^+	Ca^{++}	Mg^{++}	Cl^-	HCO_3^- in mEq./L.
NaCl	600	=	102	..	..	..	102	..
$NaHCO_3$	250	=	30	..	..	..	..	30
KCl	40	=	..	5	..	..	5	..
$CaCl_2$	28	=	..	..	5	..	5	..
$MgCl_2$	15	=	..	..	..	3	3	..
Total			132	5	5	3	115	30 mEq./L.
					145		145	
Total					290 mEq./L., or 286 mOsm./L.			
1% glucose	1,000							56 mOsm./L.
2% glucose	2,000							112 mOsm./L.
3% glucose	3,000							168 mOsm./L.

Lactic acid is added to adjust pH to 7.4.

in the rinsing fluid will lead to approximate water balance in the average patient treated with the dialyzing type of artificial kidney. The removal of edema with higher concentrations is discussed later.

2. To supply calories. During the passage of blood through the artificial kidney, glucose concentration may increase 400 mg. per 100 ml.; 48 gm. of glucose may be absorbed per hour.

VI. POSSIBLE DANGERS, COMPLICATIONS, AND UNDESIRABLE EFFECTS OF TREATMENT WITH ARTIFICIAL KIDNEY

Complications of treatment with the artificial kidney (e. g., hemolysis, clotting, and shock) have been reviewed in previous publications.[4] These early problems have been largely overcome and are now rare if technique is skillful.

A. Pyrogenic Reactions.—These have been virtually eliminated by use of new polyvinyl chloride tubing (instead of rubber tubing) and, of course, new boiled Cellophane for each patient.

‡ References 17 and 44.

B. Hemorrhage and Heparin.—Polyvinyl chloride tubing and silicone-coated glass have reduced the amount of heparin required. As a result, the formerly major danger of hemorrhage is now rarely encountered. Protamine sulfate to reverse the action of heparin is seldom required. (One milligram of protamine sulfate neutralizes 1.5 mg. of heparin.)

Despite heparinzation during dialysis, hemorrhagic diathesis, often seen in uremia and evidenced by subcutaneous or oral hemorrhage, usually responds well to treatment with the artificial kidney. It is possible that the blood used to fill the artificial kidney plays a role.

Cerebral hemorrhage has been described as a complication of treatment with the artificial kidney.§ The danger is less now that we use less heparin and prevent a rise in blood pressure during treatment. We have never seen this complication.

C. Changes in Blood Volume.—The Cellophane tubing in the rotating type of artificial kidney is filled with only a thin film of blood, but the Cellophane is distensible and the amount of blood retained in the Cellophane tubing varies. Two hundred forty milliliters of blood constantly remains in the Cellophane tubing. For each 100 ml. of blood flow per minute from the artery the blood volume in the Cellophane tubing increases 160 ml.[17] || Thus, at a flow rate of 200 ml. the blood volume in the apparatus is 560 ml. (i. e., 240 + 320 ml.). With the use of a flowmeter, changes in blood flow and, consequently, in blood volume, are easily detected.

The blood volume in the stationary artificial kidneys depends on the degree of distention of the Cellophane. With changes in pressure in the blood and rinsing-fluid compartments, changes in volume occur. In fact, the system in most stationary artificial kidneys is distensible rather than rigid. In Skeggs and Leonards' kidney, however, the changes in volume are small.

D. Technical Errors.—Technical errors could be fatal. Bleeding into the distensible Cellophane tubing, if the outflow of the rotating kidney were blocked, or bleeding through a hole in the Cellophane into the dialyzing fluid in any type of kidney could be fatal, and continuous supervision is necessary.

E. Hemolysis.—High temperature of the rinsing fluid or omission of salt from the rinsing fluid will cause hemolysis within two minutes. It is wise to mix and centrifuge a few drops of blood with rinsing fluid to detect error in composition of the fluid before the patient is connected. A mild degree of hemolysis cannot always be prevented when the rotating type of kidney is used. Usually it is barely visible. Unfortunate consequences so far have not been apparent.

F. Morphologic Changes in the Blood.—Leucopenia usually occurs during treatment with dialysis, but after a few hours the blood cell count returns to normal. De Leeuw and Blaustein [47] have shown that the leucocytes adhere to the Cellophane; the thrombocyte count is often temporarily decreased, probably for the same reason.

B. Hypertension.[48]—When blood flow through the apparatus is 200 ml. or more per minute, a rise in blood pressure is frequently observed and is sometimes alarming. With lower flow rates it is rare. An increase in cardiac output has been reported during the pressure response,[49] but this may not be the only cause. The rise in blood pressure can, if necessary, be immediately reduced with hexamethonium or by draining 300 ml. of blood into a burette along the inflow of the artificial kidney.

§ References 45 and 46.

|| At 25 revolutions per minute and 26 Cellophane threads in the Archimedes screw.

The rise in blood pressure, unwelcome as it is in most patients, has been used for treatment of otherwise refractory hypotension in patients with severe shock.[50] Frank and co-workers,[51] however, have not been able to produce a rise in blood pressure with the artificial kidney in dogs with shock that were irresponsive to other forms of treatment.

H. Relative Urinary Suppression.—In patients with chronic uremia, urine output may diminish on the day of and on the days following treatment with the artificial kidney. Merrill and his co-workers[52] added urea to the rinsing fluid to maintain the blood urea while removing retention products other than urea; they observed no reduction in urine volume and concluded that diminished diuresis is due to reduction of blood urea level. This may not be the only explanation, since diuresis is usually restored before the blood urea has returned to its former height.

If the decreased diuresis were due to diminished renal blood flow, it might be an extremely undesirable consequence of the treatment with the artificial kidney, especially in cases of acute urinary suppression, in which we have sometimes observed the same phenomenon. It will be interesting to see whether newer types of artificial kidneys will cause this temporarily diminished urine output.

I. Pulmonary Complication.—Bronchopneumonia and pulmonary edema should not be listed as complications of treatment with the artificial kidney. On the contrary, they are usually improved by dialysis, which both removes pulmonary edema ¶ and makes the patient more alert so that he will cough. Pulmonary complications may result from a suppressed cough reflex due to oversedation; codeine should not be used. Pneumonitis or poor expectoration, with subsequent anoxia, is often responsible for death in patients debilitated by uremia. Tracheotomy followed by frequent aspiration should be performed earlier in the course of treatment than has been customary.

VII. INDICATIONS FOR TREATMENT WITH ARTIFICIAL KIDNEY

A. General Principles.—At what time during uremia should treatment with the artificial kidney begin? There are two schools of thought, depending partly on the facilities available. In Boston, where an artificial kidney and team are available at any time, dialysis is used early in the course of uremia.# The dangers of such treatment are negligible, and the clinical course of the disease is much milder if uremia is relieved early. This is especially true in older patients prone to pulmonary and other complications incident to prolonged bed rest. The other approach is dictated largely by the fact that use of the artificial kidney interrupts the work of busy physicians and entails considerable expense. Thus, the artificial kidney is not employed unless it appears dangerous to wait. The artificial kidney is used only when (1) blood urea level is between 300 and 400 mg. per 100 ml., (2) serum potassium level is higher than 7 mEq. per liter, and (3) CO_2-combining power is less than 12 mEq.

The positions of both groups are justified, and I prefer the middle of the road.

The clinical conditions of patients with uremia differ immensely even if they have identical levels of retention products. The clinical condition is an important

¶ References 4, 46, and 50.

References 49, 50, and 53.

factor in determining whether treatment with the artificial kidney should be started. Characteristics of severe uremia may be progressive restlessness, irrational behavior, or stupor. These symptoms are often promptly relieved after dialysis. One should not wait until a patient is completely comatose before employing the artificial kidney. Pulmonary edema and cardiac failure have often been improved by immediate dialysis.* The extreme abdominal distention accompanying uremia also often subsides promptly after dialysis. Vomiting, which frequently makes all oral intake impossible, is nearly always less or absent after dialysis.

Potassium intoxication rarely occurs without severe renal impairment, and for this reason it is discussed here and not under the intoxications. Potassium intoxication can be relieved promptly by the artificial kidney.† The changes in the electrocardiogram [56] are reversed during the dialysis, and several authors [50] have assumed that the dialysis saved the patient's life.

The conditions listed that indicate treatment with the artificial kidney may occur in the course of acute or chronic uremia, independent of their cause. Some intoxications and edema in themselves occasionally provide an indication for use of the artificial kidney.

B. Disorders in Which the Artificial Kidney May Be Useful.—1. Acute Uremia:‡ Ischemuric episode [57] leading to acute tubular necrosis. Examples are cases of anuria following transfusion accidents, crush syndrome, shock, burns, or major operation and hepatorenal syndrome. These conditions are often erroneously called lower nephron nephrosis. Symmetrical cortical necrosis is probably an extreme form of this same syndrome.

Nephrotoxic poisoning. This may be due to corrosive sublimate, carbon tetrachloride, diethylene glycol, mushroom poisoning, potassium bichromate, uranyl nitrate, sodium potassium tartrate, potassium chlorate, or sulfonamides. Even a mixture of three sulfonamides occasionally causes renal damage.[58] The poison may be dialyzable (see Intoxications, below).

Acute glomerulonephritis. In the earlier stage of this disease it should not be treated with the artificial kidney, as Merrill [53] has observed convulsions in such patients after dialysis. However, others have had encouraging results in the late stages of severe acute glomerulonephritis.§ Treatment of uremia secondary to subacute glomerulonephritis with progressive oliguria may prolong life, but the end-result is invariably unsatisfactory.[4]

2. Acute Exacerbation of Chronic Uremia: Whether this is caused by an exacerbation of a chronic nephritis or by an intercurrent infection, operation, or intoxication, it should be treated exactly like acute uremia. Equilibrium may be restored so that a useful life is possible despite persistent chronic uremia.

3. Chronic Uremia: Goldner, Gordon, and Danzig [59] recently reported some of their results from the use of dialysis in the treatment of patients with chronic

* References 4, 46, and 50.

† References 4, 54, and 55.

‡ Several recent examples of acute uremia treated with the artificial kidney have been presented [6] in the *Transactions of the American Association of Genito-Urinary Surgeons.*

§ References 4 and 5.

renal disease. Of 20 patients having chronic uremia, who had been treated carefully before and had shown little improvement, 13 had improvement of their symptoms, which lasted an average of three days, after dialysis with the artificial kidney. Surprisingly, remission in the other seven patients lasted an average of two months. This is often longer than the "chemical" improvement lasted. Hollingsworth Smith has expressed the Boston point of view, that patients with chronic uremia deserve at least one trial treatment with the artificial kidney, since remissions may last for many months. This corroborates the experience of Alwall || in Sweden and ours.¶

4. Intoxications Without Primary Nephrotoxic Actions: Some intoxications may be treated with the artificial kidney to remove the poison by dialysis. Bromide # is more effectively removed by the artificial kidney than by the human kidneys. The tubule is unable to distinguish between Cl^- and Br^-; the clearance of Br^- thus becomes a fraction of the total halide clearance and is consequently small. The artificial kidney clears bromide according to its own concentration-gradient across the Cellophane membrane. Salicylates are well removed by dialysis.* Of the barbiturates,† some are dialyzable [65] (phenobarbital [Luminal]), some are slightly dialyzable (pentobarbital [Nembutal]), but others are almost undialyzable [65] while bound to plasma proteins (secobarbital [Seconal] and amybarbital [Amytal]).

5. Dialysis as Preoperative or Postoperative Measure: Hemodialysis is occasionally of value in preparing a patient with uremia for surgery,[50] especially if the objective of the operation is removal of the cause of the urinary suppression. In less critical cases, surgery may be performed first, followed by dialysis if recovery is not prompt.

6. Intractable Edema as Indication for Treatment: Intractable edema may occur in many clinical conditions and often complicates acute or chronic uremia. The artificial kidney of Skeggs, Leonards, and Heisler, used as dialyzer-ultrafilter,[66] can remove 1,000 to 1,200 ml. of ultrafiltrate from a patient per hour.[6] Other types of filtering and dialyzing kidneys are less effective, but they can be used.[67] Hematocrit determinations must be done during treatment to recognize too rapid dehydrations. During the ultrafiltration we find it useful to maintain the circulating plasma volume with dextran.

Since some oliguria may follow treatment with ultrafiltration, it is necessary to restrict the patient's fluid intake the following days. Sometimes diuresis follows a single treatment with a filtering-dialyzing artificial kidney.[6]

The purely dialyzing, nonfiltering types of artificial kidneys are less effective in removing edema, but by the addition of extra glucose to the rinsing fluid (1.5 to 5%) considerable amounts of fluid may be removed.[68] In this way, Lewis and others [69] induced a weight loss of 4 kg. in six hours of dialysis. However, these authors and Merrill and co-workers [50] gained the impression that high concentrations

|| References 23-29.

¶ Several reports of patients who had chronic uremia and were followed for several months or a year after dialysis (peritoneal lavage) have been published elsewhere.[14]

#References 44 and 60.

* References 45 and 61.

† References 62-64.

of glucose caused vomiting and drowsiness of the patient. This concurs with our experience. Blood sugar content may rise over 700 mg. per 100 ml., necessitating the use of small doses of insulin intravenously.

VIII. CONTRAINDICATIONS FOR TREATMENT WITH ARTIFICIAL KIDNEY

Active uncontrollable bleeding is the only absolute contraindication to treatment with the artificial kidney. Heparinization may activate gastrointestinal hemorrhages, often present in severe uremia,[70] but this is rarely serious. The ulcerations found in the rectum of patients with bichloride of mercury poisoning may bleed under the influence of heparinization. Wounds not bleeding before dialysis present a calculated risk.

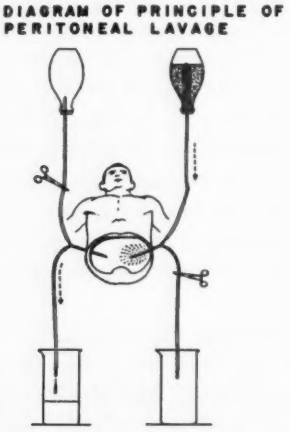


Fig. 3.—Diagram of peritoneal lavage that can be used as an intermittent and as a continuous lavage.

IX. OTHER DIALYZING METHODS: PERITONEAL LAVAGE AND INTESTINAL LAVAGE

A. Peritoneal Lavage.‡—This method is useful but is not as effective in terms of clearance as is the artificial kidney, although we once removed 203 gm. of urea with one peritoneal lavage lasting three days. Excellent clinical results in seriously ill patients have been reported by Derot and Legrain [72] and others.[71] One of the prime advantages of peritoneal lavage is that little special equipment is required. Disadvantages are uncertainty of outflow, occasional abdominal distention, and impairment of respiration or pain, the latter sometimes of several days' duration.

The technique of peritoneal lavage is simple. The bladder must be empty. Under local anesthesia a trocar is inserted through the left side of the abdominal wall at a site corresponding with McBurney's point. The stylet is withdrawn, and a snugly fitting polyvinyl chloride tube or rubber tube is inserted through the trocar into the peritoneal cavity; the trocar is then withdrawn. One and a half or 2 liters of rinsing fluid heated to body temperature is instilled into the peritoneal cavity. In Groll-

‡ References 4, 15, and 71.

man's intermittent method of lavage [9] the fluid is removed through the same cannula after two hours. However, we insert a second tube into the right side after distending the abdomen with rinsing fluid (Fig. 3), because one of the two tubes is usually blocked by intestine or omentum. Also, we prefer, as do Legrain and Merrill,[73] a continuous perfusion to an intermittent one.

The electrolyte composition of the rinsing fluid is the same as that used in the artificial kidney, except that it is sterile; oxytetracycline (Terramycin), 25 mg. per liter, is often added.

Inflow and outflow of rinsing fluid are recorded, and a fluid balance is made. Both during and at the end of the procedure, 1 or 2 liters of rinsing fluid will be trapped in the peritoneal cavity. The rinsing fluid is made more hypertonic, to attract water, if additional fluid is trapped; the glucose content of 2.5% may have to be increased to 5, 7.5, or 10%. It is also possible to remove edema fluid by the use of high concentrations of glucose.§ Pain caused by hypertonic glucose may be suppressed by addition of 50 mg. of procaine per liter of rinsing fluid. The flow should be 1 liter per hour or more. All oral intake is withheld during lavage.

When peritoneal adhesions or distention of the bowel are present, there is danger of perforating the intestine with the trocar. If this happens and the tube is left in place, surgical repair is not difficult. With prophylactic antibiotic therapy and the new method of shorter periods of dialysis (one day, at most three days), fatal peritonitis has not occurred in our patients. Peritoneal lavage requires experience, great care, and continuous supervision; but even then, overhydration, distention, and respiratory difficulties cannot always be avoided.

Indications for treatment with peritoneal lavage are the same as for treatment with the artificial kidney. "Good risks" for peritoneal lavage are patients who are dehydrated, so that fluid absorption does not immediately endanger life, and patients with little fat in omentum and abdominal wall, who consequently present few technical difficulties.

Recent abdominal operations, infections, and distention, are contraindications for peritoneal lavage.

B. Intestinal Lavage.—Gastric and colonic lavage are inefficient in removing retention products like urea. Some potassium may be removed, but use of carboxylic resins is easier and more effective. Dialysis through an isolated intestinal loop ‖ should not be attempted in the treatment of acute uremia, but it may find a place in the treatment of chronic uremia.

Dialysis employing the entire intestinal tract should be simple, but actually it is the most difficult of dialyses. While the mucosa of the intestinal tract can be used as a dialyzing membrane, it also actively absorbs and secretes, and the composition of rinsing fluid must be different ¶ from that used for peritoneal lavage or in the artificial kidney. However, those experienced in the use of this technique, like Brun [76] and Hamburger,[77] obtained results comparable to those in other forms of dialysis, although Brun has discontinued its use.

§ References 6 and 9.

‖ References 74 and 75.

¶ References 74 and 75.

X. CONCLUSION

In acute urinary suppression "conservative management" suffices for the majority of patients. However, its outcome for each individual case is unpredictable, and when it fails the dialyzing methods (artificial kidneys and peritoneal and intestinal lavage) are valuable, sometimes lifesaving adjuncts; they remove retention products and correct electrolyte imbalance, and they should not be postponed until the condition is obviously hopeless. Dialysis is occasionally useful for the elimination of some poisons and for the removal of otherwise intractable edema.

In chronic uremia, there is increasing evidence that some patients who seem to be in a so-called terminal stage can be restored to useful life for months after a single effective dialysis. This happens oftener when there has been inadequate treatment beforehand or when the condition has been aggravated by superimposed infections or other complications.

Use of plastic tubing and silicone-coated glassware in artificial kidneys has greatly reduced the amount of heparin required; consequently, danger of hemorrhage is minimized. Of the various dialyzing methods, the rotating kidney is most effective in terms of clearance; the artificial kidney of Skeggs, Leonards, and Heisler is somewhat less effective in clearance, but it can also be used as an effective ultrafilter to remove edema. Since removal of retention products is the essential function of all artificial kidneys, apparatus with low urea clearances are necessarily of limited clinical value, especially in view of the fact that other retention products are cleared so much more slowly than is urea.

Peritoneal lavage is effective but unpredictable in its outcome. It requires sterile rinsing fluid with variable concentrations of glucose. Intestinal lavage requires an entirely different chemical composition of the rinsing fluid and is the most difficult of all dialyzing methods to use.

While artificial kidneys are useful in the treatment of certain disorders, I do not recommend that many hospitals invest in expensive dialyzers, since indication for dialysis does not occur frequently enough to maintain a specially trained staff. The same is true for peritoneal lavage. Furthermore, if patients with acute anuria were transferred on the third or fourth day to special centers they would benefit from the care given by an experienced staff, even though they were not dialyzed.

ADDENDUM

We have not boiled the Cellophane at all for several recent dialyses, and there were no apparent ill effects.

Since this paper was submitted the following paper has been published:

Kolff, W. J., and Leonards, J. R.: Reduction of Otherwise Intractable Edema, Cleveland Clin. Quart. **21**:61-71 (April) 1954.

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Case Reports

CALCIFICATION WITHIN CARCINOMA OF LUNG

Report of a Case with Isolated Pulmonary Nodule

SEYMOUR B. LONDON, M.D.
AND
WILLIAM J. WINTER, M.D.
CORAL GABLES, FLA.

THE PROBLEM of the diagnosis and management of the isolated pulmonary nodule has become the subject of recent medical publications. This current interest is primarily due to the opportunity for accurate diagnosis and good prognosis offered by modern techniques of thoracic surgery. Fifteen to 30% of the surgical specimens have been found to be primary malignant lung tumors; 50%, granulomas, and the remainder, benign tumors, metastatic lesions, lung cysts, and miscellaneous lesions.* Attempts to differentiate the benign from the malignant lesion by x-ray and laboratory techniques have, with one exception, been held to be unreliable. This exception has been the x-ray characteristic of the finding of calcification within the nodule. It is generally accepted that "the presence of calcium in a pulmonary shadow is suggestive of a benign lesion" [1] and "most intrapulmonary nodules containing calcium need not be removed." [4]

Our object in reporting this case of a malignant isolated pulmonary nodule containing calcium within its substance is twofold: to demonstrate that calcification may occur in primary lung carcinoma and to suggest that calcium may be deposited within the tumor as a result of the secretory function of the carcinoma itself.

REPORT OF CASE

The patient, a 55-year-old white boat-yard superintendent, was admitted to the Coral Gables Veterans Administration Hospital, on Dec. 14, 1948, following the discovery of a solitary pulmonary lesion during an investigation for gastrointestinal complaints. The gastrointestinal symptoms, consisting of nocturnal epigastric pain, relieved by belching and change of position, were studied by gastrointestinal x-rays, and no abnormalities were found. Except for one or two respiratory infections per year, associated with a slight cough and expectoration of "tan" mucoid sputum, system review was noncontributory. There was no history of hemoptysis, chest pain, or wheeze. The past history was of significance in that the patient was hospitalized at Fort Lyons, Colo., for pulmonary tuberculosis in 1918 and was discharged six months later as an arrested case. He admitted to smoking one package of cigarettes daily for many years.

Physical examination revealed a well-developed well-nourished white man of 55 in no distress. Results of the skin, skull, and eyes, ears, nose, and throat examinations were within normal limits. The trachea was in the midline; there was no enlargement or adenopathy of the neck. The thyroid was not palpable. The chest was symmetrical; both sides moved equally and well with respiration. The lungs were clear to percussion and auscultation. No rales or wheezes were audible. The heart was not enlarged to percussion; the sounds were of good quality, and no murmurs were heard. Blood pressure was 128/84. On abdominal examination, no enlarged

From the Departments of Medicine and Pathology, United States Veterans Administration Hospital; Attending Specialist in Tuberculosis (Dr. London).

* References 1-3.

visceral organs and no masses, tenderness, or spasm were found. The prostate was smooth, nontender, and slightly enlarged by rectal examination. The extremities were normal, except for a suggestion of clubbing of the finger tips and questionable cyanosis of the nail beds.

Laboratory studies revealed a white cell count of 7,100, with 49% neutrophiles, 45% lymphocytes, 2% monocytes, and 3% eosinophiles. The red blood cell count was 4,160,000, and the hemoglobin level was 13 gm. per 100 cc. The Kahn test for syphilis was negative. The corrected sedimentation rate was 16 mm. in an hour (Wintrobe). Urinalysis showed a clear acid urine with a specific gravity of 1.016, with negative findings for albumin, sugar, and microscopic sediments. The blood chemistry values per 100 cc. revealed nonprotein nitrogen of 20.4 mg. and total protein 8.1 gm., with 4.53 gm. of albumin and 3.57 gm. of globulin.

Admission x-rays revealed a rounded, rather sharply circumscribed, nodular density, measuring 2.5 cm. in diameter, in the left midlung field. The remainder of the lung fields was clear. Comparison with an x-ray taken 18 months previously revealed that the nodule, which had been present then, had not undergone any change except for a 0.5 cm. increase in size. Films

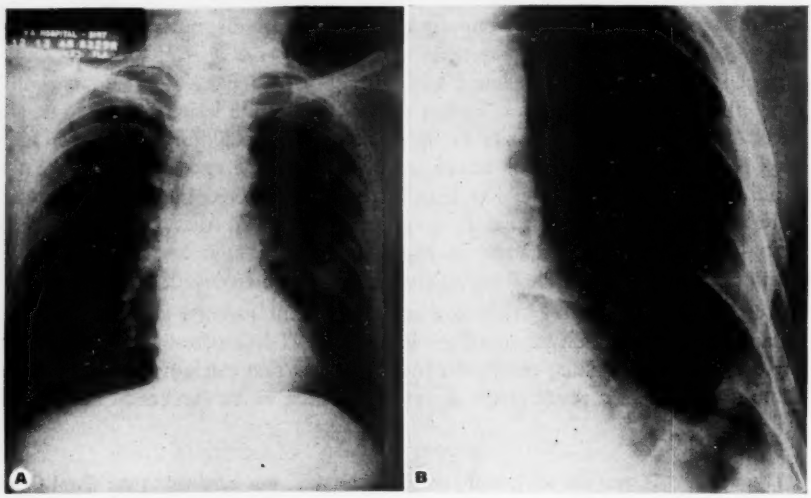

Fig. 1.—*A*, admission posteroanterior film, taken on Dec. 13, 1948, demonstrating a 2.5 cm. nodule in the left fourth anterior interspace. *B*, spot film, taken June 16, 1949, revealing calcified nodules within the tumor.

taken two months prior to admission had suggested a superimposed inflammatory interlobar pleural reaction, which had cleared spontaneously.

Because of the history of tuberculosis 30 years previously, the pulmonary nodule was strongly suspected of being a tuberculoma. Evidence supporting this contention was the demonstration by spot film and tomographic technique of the presence of calcium within the nodule (Fig. 1). Bronchoscopy was performed on three occasions, revealing a normal tracheobronchial tree, except for a moderate amount of redness and edema of the mucous membranes, consistent with chronic inflammation.

Three examinations of bronchial aspirations, in addition to four sputum cytologic examinations, were negative for malignant cells. Study of serial chest films demonstrated changes consistent with an inflammatory reaction; the margins of the nodule became irregular, and left pleural effusion developed. Two thoracenteses, of 700 cc. and 450 cc. of serosanguineous fluid, were examined for malignant cells, and none were found. Exploration of the axillary region for lymph nodes was done twice, revealing only a reactive hyperplasia on histologic examination. Smear, cultures and guinea pig inoculation of sputum, gastric aspirations, and examination of urine, chest fluid, and lymph nodes were all negative for acid-fast bacilli.

While a malignant condition had been suspected early and exploratory thoracotomy had been recommended, the patient rejected surgery because of the strong feeling that tuberculosis was the cause of the nodule and pleuritis. Streptomycin was given for 84 days as an unsuccessful "therapeutic trial." Ten months after admission the patient consented to thoracotomy, because of changes in the x-ray findings and increase of symptoms during this prolonged observation period. The thoracotomy was limited to a biopsy, because of the extensive involvement of the pleura with the pulmonary mass. After recovery from surgery, the patient gradually deteriorated and subsequently died, on June 28, 1950, three years after the discovery of the tumor and 18 months after admission.

Pathological Findings.—Microscopic Description (Surgical Specimens): The tumor was composed of alveolar spaces lined by atypical columnar cells, sometimes pseudostratified and resembling bronchiolar epithelium. Often, small papillary masses of tumor cells projected into the lumen of the alveoli. The latter were separated by narrow vascular septa, although in some

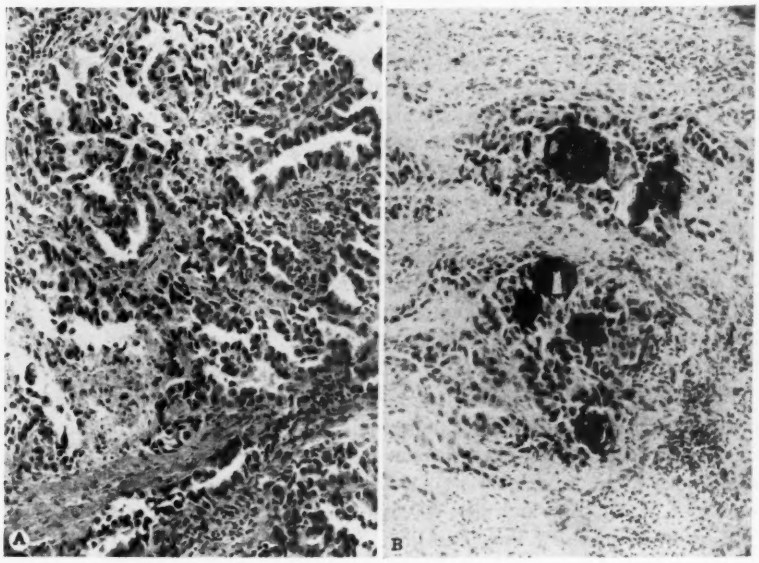

Fig. 2.—*A*, papillary adenocarcinoma, surgical specimen. Hematoxylin and eosin stain; × 55. *B*, calcified bodies within alveolar spaces lined by malignant cells. Hematoxylin and eosin stain; × 55.

areas these were considerably thickened by fibrous tissue. In several places, however, the tumor had a distinct papillary formation, such that the malignant cells lay upon stromal stalks of varying length and thickness (Fig. 2*A*). Adjacent to such areas small spherical calcified bodies, resembling psammoma bodies, occupied alveolar spaces lined by malignant cells (Fig. 2*B*). Mucicarmine stains failed to reveal mucus formation in the malignant cells, although many did contain prominent granules near their free borders which stained with the periodic acid-Schiff reaction.

Pathological Diagnosis: Papillary adenocarcinoma, with calcification, of the left lung and pleura.

Autopsy Findings: The body was extremely emaciated. A solitary tumor nodule was found in the subcutaneous tissue adjacent to the thoracotomy wound in the left chest wall. The left pleural cavity was completely obliterated by a very dense plaque-like mass of neoplastic tissue, which virtually enveloped the left lung. The latter was almost completely atelectatic. The bronchi and bronchioles were thickened and stenosed by dense tumor tissue infiltrating their walls in such a diffuse manner that no primary site could be determined. The parenchyma was

occupied by multiple cancerous nodules of varying size. The tumor had also infiltrated both the pericardium and epicardium. The liver was extensively involved, with numerous partly necrotic nodules. Metastatic lesions were also found in the kidneys and left adrenal gland. No evidence of tuberculosis was found.

Microscopically, the tumor growths had maintained the papillary and alveolar arrangement seen initially in the surgical specimen. A few calcified bodies were found in the pulmonary lesions, but none were observed in any of the metastatic tumors in other viscera.

Pathological Diagnoses.—These were (1) papillary adenocarcinoma of left lung and (2) metastatic adenocarcinoma of pericardium, liver, kidneys, and adrenal gland.

COMMENT

When this patient was first studied, it was generally believed that calcification within an isolated pulmonary nodule indicated a benign lesion. Subsequent reports supported this contention. In "Nelson's Diagnostic Roentgenology," in a discussion of the benign single nodular lung lesion, the statement is made that calcification demonstrated by Bucky or tomographic technique "excludes a malignant tumor from consideration." [5] Good and co-workers, in reviewing a large series of granulomas of the lung, state that "calcification constituted the only roentgenological assurance of benignancy." [6] Trimble, while cautioning that small flecks of calcium do not rule out carcinoma, fails to report of any instance of calcification in carcinoma of the lungs.[3] Others have expressed the general feeling, apparently on theoretical grounds alone, that it is not possible to exclude carcinoma on the basis of calcification,[7] primarily because of the possibility of incorporation of preexisting calcification into a primary lung tumor.[8] In addition to the calcification, there were other misleading indications of a benign lesion in this case, i. e., the history of tuberculosis, the unimpressive x-ray changes over an 18-month period, and the negative bronchoscopy and cytologic examinations.

Certain other well-differentiated tumors, usually papillary adenocarcinoma, may show calcium deposits within the tumor itself, probably as a result of the function of the tumor cells.[9] This phenomenon has been observed not uncommonly in pathologic specimens of papillary serous cyst-adenocarcinoma of the ovary, papillary carcinoma of the thyroid, and duct carcinomas of the breast. Liebow, in "Tumors of the Lower Respiratory Tract," in his "Atlas of Tumor Pathology," illustrates a papillary adenocarcinoma of the lung which histologically resembles ours, even to the extent of containing similar calcium nodules. He also states that "calcification may rarely be in evidence in the papillary forms." [10] The present case, therefore, represents the first detailed case report of calcification within a pulmonary carcinoma demonstrated by x-ray and histology to be an inherent part of the tumor.

SUMMARY AND CONCLUSIONS

A case is reported of an isolated pulmonary nodule containing calcium which was found to be a slow-growing well-differentiated adenocarcinoma.

The calcification which was demonstrated by x-ray was found on histologic study to occupy alveolar spaces lined by malignant cells. Therefore, it is suggested that primary adenocarcinoma of the lung may produce calcium, apparently as a result of the function of the tumor itself.

The discovery of an isolated pulmonary nodule is indication for exploratory thoracotomy in the cancer age group, despite calcification, negative bronchoscopy and cytology, and an unconfirmed history of previous lung pathology.

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News and Comment

INDEXES

This issue of the ARCHIVES appears in two parts, the second of which is the index for the preceding volume. To make the index more usable to the readers and to enable them to find information with less difficulty than has been encountered in previous volumes, the index has been broken down into three separate indexes: Title Index, Author Index, and Subject Index. The Title Index, which will take the place of the six-month Table of Contents, previously published with the index of the journals, has been prepared in such form that it can be separated from the other indexes and bound in the front of the volume. It consists of the titles of the articles arranged in alphabetical order and accompanied by the name of the author, the name of the senior author if there are more than two, the names of both authors if there are two, and the page number on which the article begins. The Author Index contains the names of all authors of articles appearing in the ARCHIVES and of the presenters of cases or papers before societies. The third index, the Subject Index, contains in alphabetical order the important subjects which have been dealt with in the volume. Individual abstracts are no longer indexed; only the categories under which they have been classified are listed. Book Notices and news items are included in this Index.

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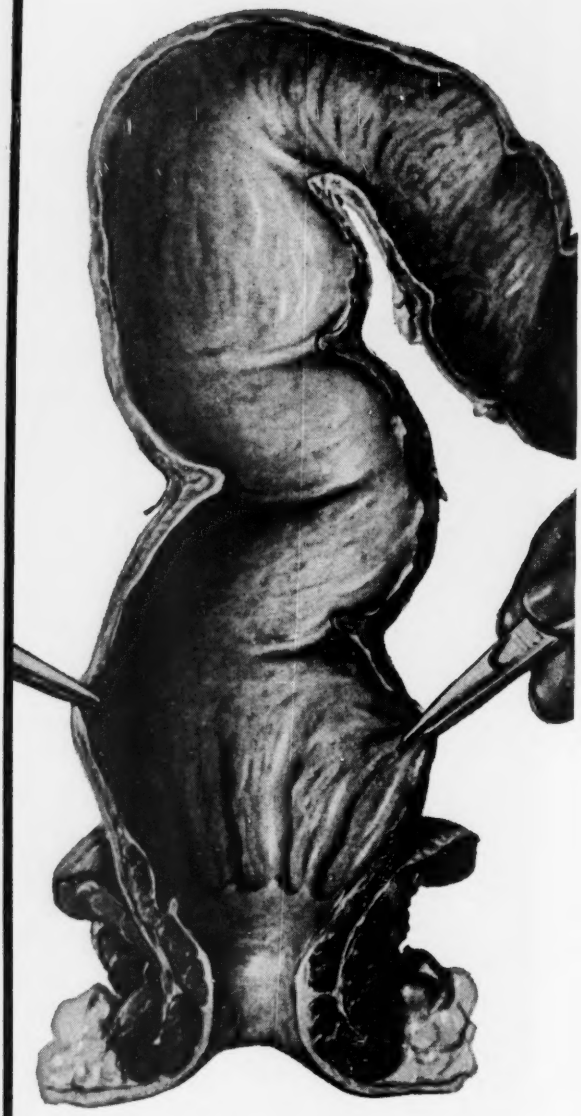

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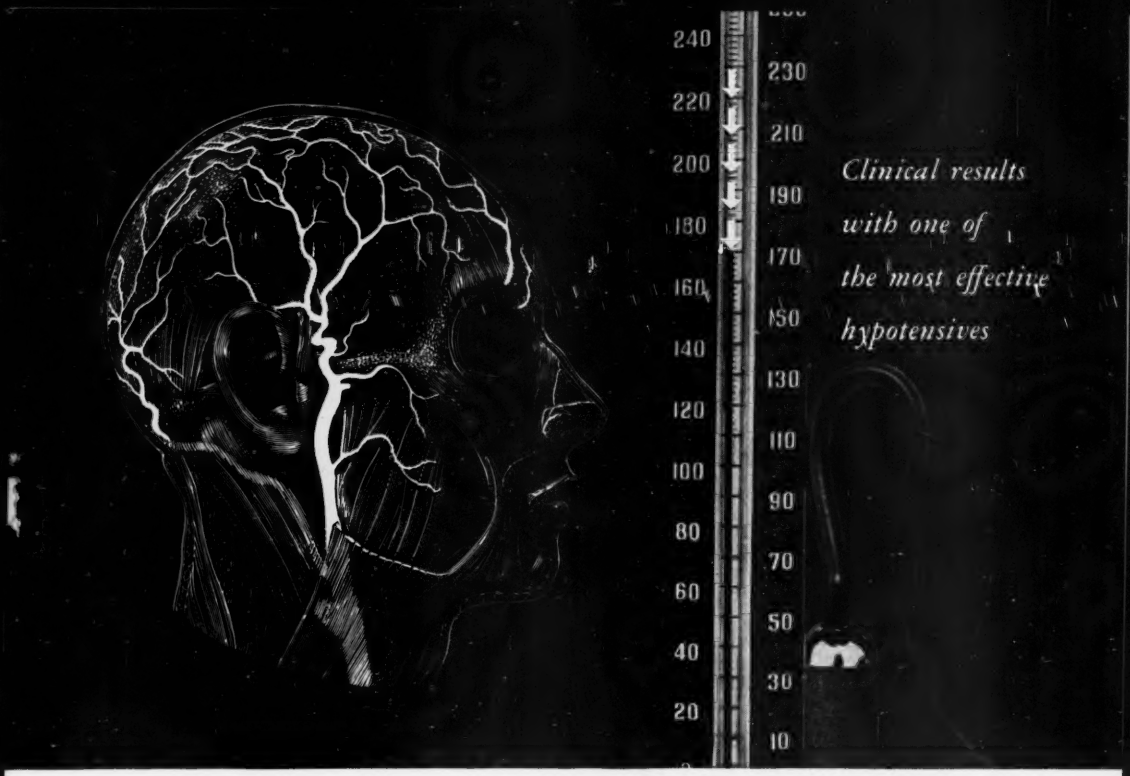

Improvement in 79% of patients with hypertensive headache[1]

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Literature and samples will be sent promptly if requested.

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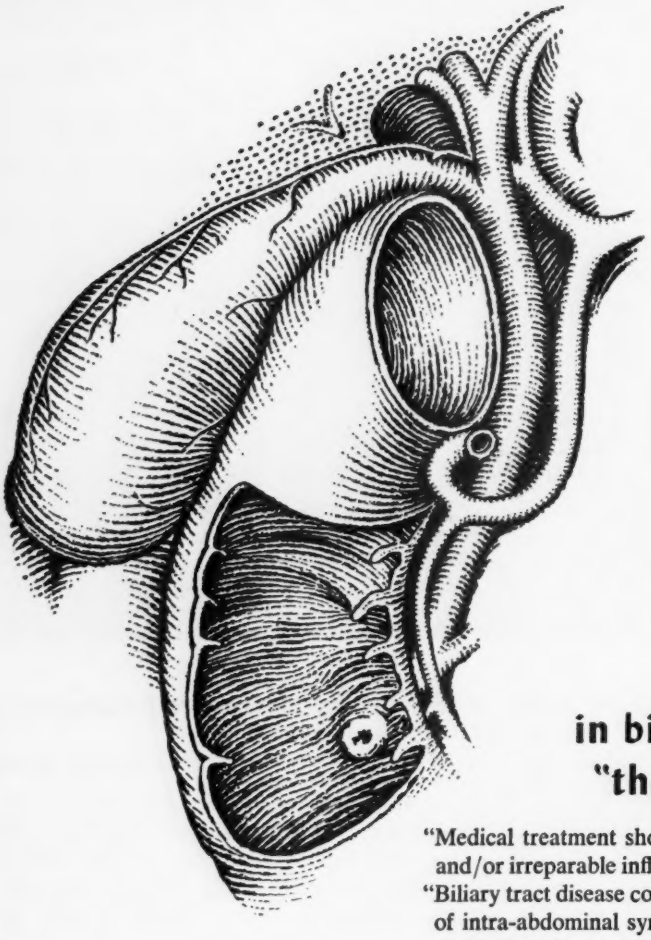

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1. Rev. Gastroenterology 20:744 (Oct.) 1953; abstract in J. A. M. A., 153:1580 (Dec. 26) 1953.

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Bargen, J. A.: Med. Clin. North America, 33:935 (July) 1949.

1950 Bargen reports that since 1949 approximately 100 patients have been treated with Azulfidine. "The results have been extremely satisfactory in most cases."
Personal communication (Apr. 12)

1951 After-control data 1949 from 119 patients treated with Azulfidine prior to 1944 showed 90 patients (84%) symptom-free or considerably improved.
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1952 In a series of 52 patients with chronic ulcerative colitis 30 or 58% showed significant improvement after treatment with Azulfidine.
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therapy is generally well tolerated with initial low dosages, gradually increased.[1,2,3] Patient response is the guide to dosage adjustment.[4] Optimal maintenance dosage level is usually reached only after 3 weeks or more; marked therapeutic effect cannot be expected with initial low dosages.[4]

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